ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 41, NO. 2 AUGUST, 1954

Contents

THIRTY-SIXTH ANNUAL SESSION—PHILADELPHIA, PA., APRIL 25-29, 1955

Subscription per annum, net postpaid, $10.00, United States, Canada, Hawaii, and Puerto Rico; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1950.

SYMPTOMATOLOGY AND TREATMENT OF APHASIA IN EVERYDAY PRACTICE

The problem of aphasia does not concern solely the specialist in neuropsychiatry but is of great interest and importance in daily office practice. Aphasia in varying degrees or forms is not at all uncommon as a sequel to some of the most frequently encountered medical and surgical conditions such as cerebral hemorrhages and thromboses, encephalitis, and other disease or injury affecting brain tissue. In many such cases seemingly insignificant symptoms are often overlooked by both patient and doctor, ultimately resulting in a permanent handicap.

Whenever an injury of brain tissue is suspected, the treating physician can make use of simple testing procedures to establish the presence of aphasia symptoms. He may then decide as to whether adequate treatment may be given at his office or whether referral to a specialized therapist is indicated.

Speech therapists Mary Coates Longerich and Jean Bordeaux explore the psychological and anatomical factors of aphasia in their recently published book *APHASIA THERAPEUTICS* (The Macmillan Company, New York, $3.75). These factors are correlated with symptomatology and with the various stages of treatment response to permit careful diagnostic and progress study.

A complete outline of a series of 28 tests, and a precise terminology of the many different manifestations of aphasia (agraphia, apraxia etc.), are included. The chapters on therapy are written in "workbook" fashion, describing step-by-step procedures in every detail.

A SYMPOSIUM ON HORMONES IN HEALTH AND DISEASE

Among the many specializations in medical practice the field of endocrinology extends perhaps farthest into everyday general practice, and into other specialties. In other words, a more than general knowledge on the subject of glands of internal secretion is required of the practicing physician in any field to help him in both diagnosis, treatment and, if necessary, proper referral.

Because of the rapid and significant changes and reorientation that have taken place in recent years in this field, it was a logical choice for The New York Academy of Medicine to select endocrinology as the topic for one of its Graduate Fortnights. The outstanding papers presented at that symposium, edited by Dr. Robert L. Craig, have now been published by The Macmillan Company in book form under the title of *HORMONES IN HEALTH AND DISEASE* ($6.00).

Among the many excellent papers contained in this volume are those dealing with the hormones' influence on the emotions, their relationship to peptic ulcer, endocrine control of metabolism, disorders of the thyroid gland, Cushing's syndrome, the management of Addison's disease, the use of steroids and gonadotropins in gynecology; the hormones of the adrenal cortex and of the anterior pituitary gland are fully discussed; the recent flurry in the use of ACTH and cortisone is brought into proper focus.

invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Tedral provides:

Theophylline	2 gr.
Ephedrine HCl	⅜ gr.
Phenobarbital	⅛ gr.

in boxes of 24, 120 and 1000 tablets

Tedral®

WARNER-CHILCOTT
Laboratories NEW YORK

You can prevent attacks in angina pectoris

Prolonged prophylaxis

Patients receiving Peritrate may obtain practical freedom from anginal attacks for from 4 to 5 hours with each dose. Russek and his colleagues[1] clearly showed that the patient-response to Peritrate was comparable to the effect produced by nitroglycerin . . . *but* the duration of Peritrate's action was "*. . . considerably more prolonged.*"

Uncomplicated prophylaxis

Prolonged protection given by Peritrate spares the patient the anxiety of waiting for pain to strike. Besides invaluable psychological support, Peritrate brightens the objective clinical picture —significant EKG improvement may be seen[1,2] and nitroglycerin need greatly reduced in most.[3] A continuing schedule of only 1-2 tablets four times a day, before meals and at bedtime, will:

1. *reduce the number of attacks in almost 80 per cent of patients*[2,3]
2. *reduce the severity of attacks which cannot be prevented.*

Available in 10 mg. tablets in bottles of 100, 500 and 5000.

References:

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT *Laboratories*, NEW YORK

When in doubt about antibacterials—

We believe you'll agree that most of them are rather good. Still, we hope you'll try Gantrisin 'Roche'...because this single sulfonamide is soluble in both acid and alkaline urine...because it has a wide antibacterial spectrum ...an impressive clinical background...and, above all, because it's so well tolerated by most patients.

Gantrisin® -- brand of sulfisoxazole

When
the patient
is in pain —

There is a new form of synthetic narcotic analgesic... less likely to produce constipation than morphine... indicated for relief of severe or intractable pain -- LEVO-DROMORAN® TARTRATE 'ROCHE'.

—*and from 1954 clinical reports*

"We agree with Waltner (1930) and Virdis (1952) that iron should be given together with cobalt to obtain the most satisfactory results."[1]

"Evidence suggests that iron and cobalt provide the most effective hematinic for pregnant women."[2]

"The babies were closely observed daily for ill effects of the medication while at the premature unit and when they returned for check-ups. None of them showed harmful effects despite the large doses."[3]

***Bibliography of 192 references available on request.**

1. Coles, B.L., and James, U.: The Effect of Cobalt and Iron Salts on the Anaemia of Prematurity, Arch. Disease in Childhood *29*:85 (1954).
2. Holly, R.G.: The Value of Iron Therapy in Pregnancy, Journal-Lancet *74*:211 (June) 1954.
3. Quilligan, J.J., Jr.: Effect of a Cobalt-Iron Mixture on the Anemia of Prematurity, Texas St. J. Med. *50*:294 (May) 1954.

Roncovite

The original, clinically proved, cobalt-iron product.

SUPPLIED

RONCOVITE TABLETS

Each enteric coated, red tablet contains:
Cobalt chloride..... 15 mg.
Ferrous sulfate exsiccated.....0.2 Gm.

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:
Cobalt chloride..... 40 mg.
(Cobalt....9.9 mg.)
Ferrous sulfate..... 75 mg.

DOSAGE

One tablet after each meal and at bedtime; 0.6 cc. (10 drops) in water, milk, fruit or vegetable juice once daily for infants and children.

LLOYD

BROTHERS,

INC. *Cincinnati 3, Ohio*

In the Service of Medicine Since 1870

Upjohn

For the many thousands of patients with essential hypertension, there is new hope for longer, happier lives. RESERPOID* (Upjohn brand of reserpine) is the active, pure alkaloid of Rauwolfia serpentina. In just 1/1000 mg., Reserpoid matches the potency of 1

*TRADEMARK

Upjohn

mg. of the whole root... Reserpoid carries non-hypnotic sedation and bradycardic action along with its principal antihypertensive effect. It is a persistently pleasant drug: usually even before the pressure falls, a sense of calm settles over the anx-

ious and irritable hypertensive. Lowering of the pressure is gradual, which gives the patient a week or more to adjust to the new levels. Reserpoid acts centrally upon the autonomic nervous system. It is not a ganglionic blocking agent, does not induce

postural hypotension . . . Reserpoid has no presently defined contraindications. It is ideal for the "average" case—that large group of mild and moderate hypertensives who have symptoms, but no demonstrable pathology. In severe hypertension with advancing vas-

Upjohn

cular damage, Reserpoid is valuable in augmenting and stabilizing the effects of other, more drastic drugs—making their smaller dosage possible. Reserpoid therapy is not encumbered by the difficulties of delicate titration. Just 1 mg. of Reserpoid daily, taken in

2 two-way control of hay fever

1. shorter and safer desensitization procedures with

CHLOR-*TRIMETON* Injection 100 mg./cc.

(in same syringe with allergenic extract)

2. relieve symptoms—all day (or all night*) relief with just one

CHLOR-*TRIMETON* REPETAB (8 mg.)

*If sleep is a problem, prescribe CHLOR-*TRIMETON* REPETABS with Sodium Pentobarbital (¾ gr.)

CHLOR-*TRIMETON*® Maleate, brand of chlorprophenpyridamine maleate.
REPETABS,® repeat action tablets.

Schering

CHLOR-*TRIMETON*

whole-root Raudixin:

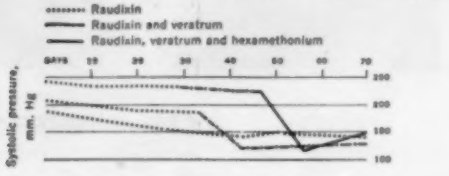
safe, smooth, gradual reduction of blood pressure

Raudixin is the most prescribed of rauwolfia preparations. It is *powdered whole root* of Rauwolfia serpentina—not just one alkaloid, but all of them. Most of the clinical experience with rauwolfia has been with Raudixin.

Raudixin lowers blood pressure in gradual, moderate stages. "A sense of well-being, decrease in irritability, 'improvement in personality' and relief of headache, fatigue and dyspnea" are frequently described by patients.[1]

Raudixin is base-line therapy. In mild or moderate cases it is usually effective alone; "...when rauwolfia is combined with other hypotensive agents, an additive hypotensive effect frequently is observed even in severe hypertension."[2] "It produces no serious side effects. It apparently does not cause tolerance."[1] 50 and 100 mg. tablets, bottles of 100 and 1000.

Raudixin alone and combined with other hypotensive agents



Raudixin Squibb rauwolfia

SQUIBB

1. WILKINS, R. W., AND JUDSON, W. E.: NEW ENGLAND J. MED. 248:48, 1953.
2. FREIS, E. D.: M. CLIN. NORTH AMERICA 38:1163, 1954.

"RAUDIXIN"® IS A TRADEMARK

Clinicopharmacologic Properties of Gitaligin® [Amorphous Gitalin]

The following table is quoted verbatim from the report by Dimitroff, S.P.; Griffith, G.C.; Thorner, M.C. and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure, Annals Int. M. 39:1189 (Dec.) 1953.

Derivation	*Digitalis purpurea.*
Appearance	Amorphous white powder.
Uniformity	Constant from batch to batch.
Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
Dissipation	Rate of excretion between the rapidly excreted Digoxin and slowly excreted leaf or digitoxin.
Range of toxicity	Less toxic than other glycosides. Digitalizing dose is about 1/3 amount of the toxic dose.
Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4-6 hours until toxic or therapeutic effect appears (usually 24-48 hours.)
Dosage by slow method	A single dose of 1.5 mg. daily, or 0.5 mg. t.i.d. until toxic or therapeutic effect appears (usually 4-7 days).
Symptoms of toxicity	Same as for other glycosides, i.e., anorexia, nausea, vomiting, color-vision, ectopic beats, ST-T changes.

WHITE LABORATORIES, INC., Kenilworth, N.J.

Simple dosage equivalent: 0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf. Gitaligin is supplied in 0.5 mg. tablets, deep scored for accuracy and flexibility of dosage—in bottles of 30 and 100.

Gitaligin is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

THE AMERICAN COLLEGE OF PHYSICIANS

SCHEDULE OF POSTGRADUATE COURSES, AUTUMN, 1954

(All registrations must be made through the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. Fees: A.C.P. Members, $30.00; non-members, $60.00. Registration forms furnished on request. Detailed bulletins available from August 1, 1954.)	October				November				December				
	4–9	11–16	18–23	25–30	1–6	8–13	15–20	22–27	29–Dec. 4	6–11	13–18	20–25	27–31
Course No. 1, **SELECTED PROBLEMS IN INTERNAL MEDICINE:** University of Oklahoma School of Medicine, Oklahoma City, Okla.; Wann Langston, M.D., F.A.C.P., Director.	X							Thanksgiving Week—Thanksgiving, November 25					
Course No. 2, **BASIC CONCEPTS IN INTERNAL MEDICINE:** Medical College of Virginia, Richmond, Va.; Charles M. Caravati, M.D., F.A.C.P., and Kinloch Nelson, M.D., F.A.C.P., Co-Directors.		11–15											
Course No. 3, **NEWER DEVELOPMENTS IN CARDIOVASCULAR DISEASES:** Mount Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors.		11–15											
Course No. 4, **MEDICAL ASPECTS OF NEOPLASTIC DISEASES:** Memorial Center for Cancer and Allied Diseases, New York, N. Y.; Cornelius P. Rhoads, M.D., F.A.C.P., and Rulon W. Rawson, M.D., F.A.C.P., Co-Directors.			18–22										
Course No. 5, **SELECTED SUBJECTS IN INTERNAL MEDICINE:** University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Roy R. Snowden, M.D., F.A.C.P., Director; Frank J. Gregg, M.D., F.A.C.P., Co-Director.				X									
Course No. 6, **PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE:** University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director.					1–5								
Course No. 7, **INTERNAL MEDICINE:** Beth Israel Hospital, Boston, Mass.; Herrman L. Blumgart, M.D., F.A.C.P., Director.						8–12							
*Course No. 8, **GASTRO-ENTEROLOGY:** University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.						8–12							
Course No. 9, **A SURVEY OF RECENT DEVELOPMENTS IN THE CARDIOVASCULAR FIELD:** Michael Reese Hospital, Chicago, Ill.; Louis N Katz, M.D., F.A.C.P., Director.										X			

* Please note that this course is being given one week earlier than originally scheduled.

ANNALS OF
INTERNAL MEDICINE

VOLUME 41 AUGUST, 1954 NUMBER 2

FURTHER OBSERVATIONS ON PATIENTS WITH SEVERE HYPERTENSION SUBJECTED TO ADRENAL RESECTION AND SYMPATHECTOMY *

By WILLIAM A. JEFFERS, F.A.C.P., HAROLD A. ZINTEL, F.A.C.S., A. GORMAN HILLS, JOSEPH H. HAFKENSCHIEL, STEPHEN B. LANGFELD, ALFRED M. SELLERS, and CHARLES C. WOLFERTH, F.A.C.P., *Philadelphia, Pennsylvania*

INTRODUCTION

IT has now been four years since our first patient was submitted to adrenal resection and three years since the first report to this College.[1] We are aware that it may well require more than 10 years of careful study before the merits of this type of surgical approach can be properly evaluated. Meanwhile, the need for less drastic and more effective means of altering the course of severe hypertension remains obvious.

As indicated previously,[2, 3] our interest has become focused upon the effects of total or subtotal adrenal resection combined with a limited Adson-type sympathectomy. Our immediate objective remains a comparison of the course of the 96 surviving patients so treated with that of those subjected only to adrenalectomy,[4, 5] or to thoracolumbar sympathectomy alone,[6] or to thoracolumbar sympathectomy combined with adrenalectomy.[2, 3] Patients surviving various combinations of sympathectomy and adrenalectomy other than total or subtotal adrenalectomy and Adson-type sympathectomy now number only 29. Since they comprise a small and heterogeneous group, they will be referred to as "Other" in our accompanying tables, and

* Presented at the Thirty-Fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 9, 1954.

From the Edward B. Robinette Foundation, Medical Clinic and the Surgical Service of the Hospital of the University of Pennsylvania.

This investigation was supported in part by research grants from The National Heart Institute, the U. S. Public Health Service (H-338), the Squibb Institute of Medical Research, Eli Lilly and Company, Ciba Pharmaceutical Products, Inc., and Merck and Company, Inc.

emphasis will be placed upon the gradually increasing numbers of patients who have had an Adson-type sympathectomy and either total or subtotal adrenalectomy. It is the purpose of this report to offer another year's perspective concerning these patients and to point out certain phenomena which have appeared since our last report.

As of March 1, 1954, 125 patients have submitted to various types of adrenal resection and sympathectomy as a part of this study. Ninety-six patients have survived. Of the 96 survivors, 17 have been followed for a period of less than six months. Accordingly, the tabular summaries will include as "?" these patients and a few others in whom adequate follow-up has not been possible during the past year in spite of repeated attempts to obtain more specific information about them. Seventy-three surviving patients have been followed for from six to 36 months. Six of them have been followed for between 36 and 48 months. Among the 29 who failed to survive, the causes of death have been as follows: stroke, 16; coronary occlusion, 6; uremia, 4; adrenal insufficiency, 1; other, 2.

Evaluation of Blood Pressure Response

Our observations suggest that clinical improvement does not necessarily parallel the change in blood pressure noted after operation. As in the case of sympathectomy, certain patients may do well clinically despite the persistence of considerable elevations of blood pressures. Conversely, four patients in our series have suffered fatal late cardiovascular complications despite an excellent blood pressure response. In an attempt to correlate

Table I

Classification of Results
Blood Pressure—Supine or Standing

A—Excellent. Not more than 150/100
B—Fair. 155/100 to 189/110
C—Poor. 185/115 to 200/120
D—Failure. More than 200/120

changes in blood pressure with other clinical features, we have used a *revised* classification of patient's responses: A—Excellent; B—Fair; C—Poor; D—Failure (table 1). The symbols A, B, C, and D are accordingly incorporated as a part of the tabular summaries. It should be emphasized that criteria for this classification have been altered somewhat since our previous reports,[2, 3] to allow the symbols to refer to a definite range of blood pressures.

Indications and Contraindications

In selecting patients for operation we have attempted to test the validity of our previous criteria by making occasional exceptions and observing the result. As yet we have not found reason to change the following:

Indications: (1) Average diastolic pressure of 120 mm. of mercury or more; (2) failure to respond to intensive medical therapy; (3) evidence of

progressive damage to the heart, kidneys, brain or eyes. All three of these indications should be present before operation is resorted to.

Contraindications: Any one of the following appears still to be a contraindication: (1) impaired renal function, with excretion of less than 20 per cent of phenolsulfonphthalein 15 minutes after injection, and/or a blood urea nitrogen of over 20 mg. per cent; (2) recovery from a stroke or coronary occlusion for less than six months; (3) age beyond 55 years; (4) inability to coöperate closely following operation because of intellectual deficit or emotional instability.

TABLE II

Effects of Various Limiting Factors upon Postoperative Result

	Number of Patients	Percentage Mortality	Percentage A+B	Percentage C+D+?
Smithwick Group 4	59	29	42	29
Diastolic BP less than 140 BUN less than 20 15 min. PSP more than 15%	75	11	64	25
Diastolic BP more than 140 BUN less than 20 15 min. PSP more than 15%	26	27	35	38
Diastolic BP less than 140 BUN less than 20 15 min. PSP less than 15%	7	43	57	0
Diastolic BP more than 140 BUN less than 20 15 min. PSP less than 15%	5	60	20	20
Diastolic BP more than 140 BUN more than 20 15 min. PSP less than 15%	7	57	29	14

The lowest mortality (11%) and highest proportion (64%) of good BP responses are seen when all factors are favorable. When there is a combination of diminished PSP excretion with elevation of diastolic BP over 140, and with a BUN of over 20, the mortality is high (57–60%), and the proportion of good BP responses is small (20–29%). Those patients for whom adequate information is not available are listed as (?).

The validity of the contraindications with respect to renal function is illustrated by table 2. It shows the course of patients who have been operated upon with and without high levels of diastolic pressure and evidences of impaired renal function. The most favorable mortality (11 per cent) and blood pressure responses were observed among those 75 patients having an average diastolic pressure of less than 140 mm. Hg prior to operation, with phenolsulfonphthalein excretion greater than 15 per cent in the first 15 minutes, and blood urea nitrogen less than 20 mg. per cent. Marked elevation of diastolic pressure (26 patients) appeared to decrease life expectancy. Mortality was still higher among the seven patients with a phenolsulfonphthalein excretion of less than 15 per cent in 15 minutes,

TABLE III

Postoperative Blood Pressure Response in Relation to Type of Operation Performed

Type Operation	Number of Patients	A	B	C	D	?	Dead
SA–AD	56	22	9	5	4	4	12
TA–AD	40	11	10	4	3	7	5
Other	29	9	4	3	0	1	12
Total	125	42	23	12	7	12	29 (23%)
% of 96 living		44	24	12	7	12	

SA—subtotal adrenalectomy. TA—total adrenalectomy. AD—Adson sympathectomy. See table 1 for meaning of A, B, C, D. Of the 96 survivors, 44 + 24 (or 68%) have shown an excellent or fair response. Those patients for whom adequate information is not available are listed as (?). 23% of the 125 have failed to survive.

even if the diastolic blood pressure did not exceed 140 or the blood urea nitrogen exceed 20 mg. per cent; but those who survived have shown a favorable blood pressure response. Survival and blood pressure responses were poorest when patients were operated upon in the presence of diastolic blood pressures over 140 and impaired phenolsulfonphthalein excretion (five patients), and with these two factors plus nitrogen retention (seven patients).

RESULTS

Table 3 lists the numbers of patients subjected to various types of sympathectomy and adrenalectomy, together with the mortality for each group and the response with respect to blood pressure. Emphasis is again placed on those who have had either total or subtotal adrenalectomy in connection with Adson-type sympathectomy. Among the 96 survivors the blood pres-

TABLE IV

Classification of Postoperative Result in Relation to Preoperative Smithwick Group

		Result Number of Patients					
Smithwick Group	Number of Patients	A	B	C	D	?	Dead
1	0	0	0	0	0	0	0
2	32	15 (47%)	6	3	1	4	3 (10%)
3	34	13 (38%)	6	1	1	4	9 (26%)
4	59	14 (24%)	11	8	5	4	19 (32%)
Total	125	42	23	12	7	12	29

See table 1 for meaning of A, B, C, D. Despite the high mortality (32%) among Group 4 patients, 42% of them have had an excellent or fair response.

sure response, percentile, has been as follows: A, 44; B, 24; C, 12; D, 7. The over-all mortality has been 23 per cent. The operative mortality (within one month of operation) is 6.4 per cent. Table 4 shows the mortality and blood pressure response in relation to the preoperative Smithwick [6] grouping. With ascending Smithwick rating the mortality has increased and the proportion of excellent blood pressure responses has de-

TABLE V

Incidence of Changes in Electrocardiograms Postoperatively, 96 Patients

Type Operation	Improved	Same	Worse	?
SA–AD	19	19	1	5
TA–AD	12	14	1	8
Other	4	7	5	1
% of 96	37	42	7	14

"Improved" includes a progressive tendency for abnormalities of the QRS and T waves to revert toward normal. 37% of patients show improvement, whereas 7% have developed further abnormalities. See table 3 for abbreviations SA–AD, TA–AD.

creased. Tables 5, 6 and 7 summarize the changes in electrocardiogram, heart size and ocular fundi which have been observed in the 96 surviving patients during the past four years. There has been some consistency in the degree of improvement with respect to these three features. Only a few patients have demonstrated clinical evidence of deterioration following operation. This is in contrast to the larger percentage who have had a poor ("C" or "D") response in blood pressure (table 2). Those listed as "Same"

TABLE VI

Incidence of Changes in Heart Size Postoperatively, 96 Patients

Type Operation	Improved	Same	Worse	?
SA–AD	15	18	3	8
TA–AD	11	16	0	8
Other	7	9	0	1
% of 96	34	45	3	18

"Improved" indicates a persistent diminution in the heart's frontal area or transverse diameter. See table 3 for abbreviations SA–AD, TA–AD.

include all degrees originally observed, but without change subsequent to operation.

Congestive Heart Failure: Those patients who had exhibited congestive heart failure prior to operation, and who survived, have continued to do well without salt restriction, digitalis or other diuretic measures. These now number 16. There were, however, 11 patients who had congestive failure preoperatively and who have succumbed to other causes of death.

Angina Pectoris: Of 24 surviving patients who had angina pectoris prior to operation, 17 have been relieved of this symptom.

Renal Function: There continues to be little or no evidence of improvement in renal function following operation: of 56 patients with a preoperative phenolsulfonphthalein excretion of 25 per cent or more in the first 15 minutes of the test, only 26 have maintained as good a result subsequently. Of the 96 surviving patients, only four had slight elevations of blood urea nitrogen prior to operation, whereas in 21 there have been elevations of over 20 mg. per cent subsequently. It must be pointed out, however, that elevation of the blood urea nitrogen in these individuals may be an evidence of *adrenal* insufficiency, with or without other chemical disturbances such as hyperkalemia. Routine urinalyses, however, show some improvement: prior to operation, 26 patients showed more than a trace of albumin, whereas this has been the case subsequently in only three; cylindruria was present in 44 patients preoperatively, and in only eight postoperatively. There has as yet been no apparent relationship between blood pressure levels and changes in renal function observed late in the postoperative course.

TABLE VII

Incidence of Changes in Ocular Fundi Postoperatively, 96 Patients

Type Operation	Improved	Same	Worse	?
SA–AD	22	15	0	7
TA–AD	12	14	1	8
Other	10	6	0	1
% of 96	46	37	1	16

"Improved" indicates a persistent decrease in the grade of retinopathy. See table 3 for abbreviations SA–AD, TA–AD.

Headache: This symptom was prominent in 51 patients, but has disappeared following operation in all save 15.

Need for Replacement Therapy: Following subtotal adrenalectomy in 57 surviving patients, 15 are now able to be without adrenal cortical replacement therapy. The observation that 11 of these continue to show an A or B blood pressure response is interpreted as evidence against the possibility that there has been regeneration of the remaining adrenal fragment. Conversely, three patients whose blood pressures remained markedly elevated following subtotal adrenalectomy have shown reductions in pressure when the remaining adrenal fragment was reduced in size or removed at a third-stage operation. As before,[2, 3] those subjected to total adrenalectomy are usually given the following: cortisone, 25 to 50 mg. in divided dosage daily; DCA, 2 mg. buccally daily, and enteric-coated tablets of sodium chloride, 3 to 6 gm. daily. Once the optimal dosage is established changes are seldom necessary, save for the exceptions which are discussed elsewhere with respect to operation, infections or seasonal variations in the temperature.

Tendency Toward Blood Pressure Relapse: We have previously indicated that patients subjected to procedures of this sort should be observed

for many months before the effects of operation can be evaluated. With respect to the response in *blood pressure*, however, it is apparent that a change in the trend is rather uncommon after six months: among the 96 survivors, 12 who showed C or D results at the end of six months have subsequently shown improvement, but in five of these improvement followed the use of depressor drugs. Conversely, only three with an A or B result at six months have subsequently relapsed to show more severe hypertension. The rarity of relapse to date appears to be in contrast to the behavior of patients subjected to thoracolumbar sympathectomy.[7] It is interpreted also as evidence against regeneration of the adrenal fragment in those subjected to subtotal adrenalectomy. Again, it should be pointed out that the entire postoperative course, rather than levels of blood pressure per se, should be the basis for evaluating the response to operation.

Late Sequelae of Operation: Among the 96 surviving patients the following sequelae have occurred with sufficient frequency to deserve mention: intolerance to cold, 19; mild Raynaud's phenomenon, 18; pigmentation of the skin, 21; failure of ejaculation in males without other evidence of sexual dysfunction, 15. The last is the expected result of bilateral lumbar sympathectomy. Raynaud's phenomenon, likewise, is probably the result of "compensatory" sympathetic overactivity in the upper extremity.

A tendency toward excessive weight gain, without edema, is becoming apparent as a late postoperative phenomenon. This seems to vary with the dose of cortisone used. We plan to explore other types and schedules of replacement therapy during the coming year in an attempt to avoid this.

In a few patients studied preoperatively and postoperatively [8] a metabolic acidosis has been observed late after operation, with an increased arterial blood hydrogen ion concentration and diminished whole blood buffer base. This may be related more to the effects of replacement therapy than to the result of extensive adrenal resections.

To date we have not observed an unusual susceptibility to respiratory or other infections. Hospitalization has been recommended in the event of a febrile illness, or for such surgical procedures as dental extractions. At such times it has appeared advisable to provide a considerable excess (100 mg. daily) of cortisone.

Fifteen patients showing marked elevations of blood pressure postoperatively have been subjected to prolonged trials with the depressor agents protoveratrine, hydralazine and reserpine. Seven have shown improvement. In three instances improvement by two grades (e.g., from C to A) has occurred. These seven patients are included in table 3 according to their current blood pressure levels *while receiving depressor therapy*.

Two patients have become pregnant.[9] One was normotensive following operation, remained so, and was delivered of a normal infant. The other had remained severely hypertensive following operation, and suffered a miscarriage in the seventh month of pregnancy. Despite depressor therapy, her blood pressure has continued to be markedly elevated.

Discussion

It is appropriate and essential to repeat the precautions which we have previously emphasized:[2] "Operations of this sort, on this type of patient, cannot be attempted without a well integrated medical and surgical team who are prepared to deal not only with all surgical complications, but also with any and all of the manifestations of severe hypertensive cardiovascular disease and adrenal insufficiency. A prolonged and careful follow-up is obligatory for each patient. Patients must be warned repeatedly that anorexia, nausea or vomiting means adrenal insufficiency and demands emergency treatment. They must also learn to report promptly to their physicians the occurrence of a cold or other febrile or infectious illness. During the summer months their requirements for cortisone, DCA and salt will be somewhat larger than during cool weather. A member of the team must be on call at all times, prepared to treat acute adrenal insufficiency or other emergency."

Table VIII

Mortality in Six Series of Patients Subjected to Various Operative Procedures for Hypertension

	Grimson[13] "Total" Sympathectomy	Smithwick Thoracolumbar Sympathectomy	Zintel Thoracolumbar Sympathectomy (to be published)	Zintel Combined Adrenalectomy and Sympathectomy	Thorn[4] and Harrison Total Adrenalectomy	Bowers[5] Subtotal Adrenalectomy
Number of patients	172	1,266	77	125	15	27
Period of postoperative observation	5 to 10 years	At 5 years	3 to 7 years	Less than 4 years	Less than 2 years	Less than 22 mos.
Percentage of mortality	16.7	21.5	26	23	47	40
Average Smithwick grade	?	2.3	3.2	3.2	?	?

This illustrates the difficulty of attempting comparisons, when the preoperative status of patients is not considered. See table 9 for a more precise comparison of Smithwick's results and ours. Most of Thorn's patients had severe kidney damage.

In addition to clinical examinations of the type herein reported, careful metabolic studies are also being performed on these patients.[10, 11] They offer a unique opportunity to study various problems in adrenal physiology.

We have attempted to characterize as clearly as possible the patients we have chosen for operation, by stating our indications and contraindications, and by presenting the positions of our patients in the Smithwick classification. In this fashion we hope to avoid the difficulty usually encountered in attempting to compare reports from various clinics concerning therapy proposed for hypertension. This difficulty became evident when we tried to compare even such simple features as mortality (table 8) with series reported other than Smithwick's.[6]

A somewhat better comparison is possible between our patients subjected to combined adrenalectomy and sympathectomy and those who have had only thoracolumbar sympathectomy in Smithwick's or Zintel's series (table 9). It will be noted that the lowest mortality, to date, among patients in Smithwick Group 4 has occurred after combined sympathectomy and adrenalectomy. These results are only preliminary. *If this trend persists,* it may indicate that *adrenalectomy* and *subdiaphragmatic sympathectomy* can be performed with greater safety and effectiveness in poor risk patients than can thoracolumbar sympathectomy. Such a conclusion, however, is not justified on the basis of this analysis because of the comparatively brief period of observation of patients now living who have had adrenalectomy and sympathectomy. It is already apparent that convalescence is briefer and less painful when only a subdiaphragmatic operation is performed, as compared with thoracolumbar sympathectomy. The proportions of 96 surviving patients who have been observed for various periods of time are as follows: less than one year, 32 per cent; one to two years, 32 per cent; two to three years, 30 per cent; three to four years, 6 per cent.

TABLE IX

Mortality in Three Series of Patients, Subjected Either to Thoracolumbar Sympathectomy or to Combined Sympathectomy and Adrenalectomy

Smithwick Group	Thoracolumbar Sympathectomy Smithwick		Thoracolumbar Sympathectomy Zintel		Combined Sympathectomy-Adrenalectomy Zintel	
	Number of Patients	% Mortality at 5 years	Number of Patients	% Mortality at 5 years	Number of Patients	% Mortality, 1 mo. to 4 years
1	158	8	2	0	0	0
2	735	13	20	5	32	10
3	244	20	17	6	32	22
4	129	59	38	47	61	31
Total	1,266	19	77	26	125	23

Note gradually increasing mortality in ascending Smithwick groups. It will also be noted that the lowest mortality to date among patients in Smithwick Group 4 has occurred after combined sympathectomy and adrenalectomy, but 32% of 96 surviving patients so treated have been observed for not longer than 1 year, 32% for from 1 to 2 years, 30% for from 2 to 3 years, and 6% from 3 to 4 years.

SUMMARY

1. A further report is presented concerning the clinical course of severely hypertensive patients subjected to adrenal resection and sympathectomy. This is a review of 125 patients, observed for from six months to four years.

2. Attention is directed toward the 96 patients operated upon with an Adson-type sympathectomy and either total or subtotal adrenalectomy.

3. During a maximum of four years' observation, 23 per cent of the 125 patients have died. The cause of death in more than half of these was a stroke.

4. Evidence is presented for continuing to adhere to indications and contraindications for operation as previously chosen. Marked impairment of renal function remains the most definite contraindication.

5. Blood pressure responses among the 96 survivors following operation are adjudged to be as follows: excellent, 44 per cent; fair, 24 per cent; poor, 12 per cent; failure, 7 per cent.

6. Improvement in the electrocardiogram (37 per cent), heart size (34 per cent), and ocular fundi (46 per cent) continues to be gratifying. There has been little evidence of progressive vascular damage in these areas following operation.

7. Among the 96 survivors relief of congestive heart failure (100 per cent), angina pectoris (71 per cent), and headache (70 per cent) have been observed.

8. As measured by phenolsulfonphthalein tests and blood urea nitrogen, progressive impairment of renal function may occur occasionally, without regard to the postoperative blood pressure response. Elevation of the blood urea nitrogen above 20 mg. per cent in these patients is sometimes evidence of *adrenal* rather than *renal* insufficiency. Unequivocal improvement in renal function has not been found among postoperative patients to date.

9. Of 57 patients having a subtotal adrenalectomy, 15 (26 per cent) now require no adrenal cortical replacement therapy. The course of these 15 patients does not suggest that regeneration of the remaining adrenal fragment has occurred.

10. Those patients subjected to total adrenalectomy require cortisone, 25 to 50 mg., DCA, 2 mg., and sodium chloride, 3 to 6 gm. daily. A tendency toward progressive weight gain with such a regimen makes it desirable to explore the use of other agents and schedules of dosage.

11. Among the 96 surviving patients the following sequelae have occurred with sufficient frequency to deserve mention: intolerance to cold, 19; mild Raynaud's phenomenon, 18; pigmentation of the skin, 21; failure of ejaculation in males, 15.

12. Of 15 patients showing persistent and marked elevations of blood pressure postoperatively, seven have shown improvement while receiving such drugs as protoveratrine, hydralazine and reserpine.

13. It is again emphasized that this is an experimental approach, which cannot at present be recommended as a treatment for hypertension. It cannot be pursued safely without a well integrated medical, surgical and laboratory team, and close observation throughout the entire postoperative course. As in the case of sympathectomy, one cannot predict which patients will respond with improvement, nor can we discern why certain patients with adequate renal function have failed to improve after operation. A few patients whose blood pressure responses were excellent following operation have succumbed to vascular accidents not withstanding.

14. A preliminary attempt is made to compare the mortality of these patients with that of those subjected to adrenalectomy alone and with thoracolumbar sympathectomy.

ACKNOWLEDGMENTS

Merck and Company, Inc. has supplied the large amounts of aqueous suspension and tablets of Cortone used in this study. The Ciba Company and The Schering Company have furnished DCA for both oral and parenteral use.

Dr. Francis C. Wood and Dr. I. S. Ravdin continue to give their wholehearted support to this project.

A large share of the credit for our low operative mortality must go to Dr. Robert D. Dripps, Dr. James E. Eckenhoff, Dr. Leroy D. Vandam and their associates in the Department of Anesthesiology.

Janet Merrill Roeder and Henrietta Brandt have worked tirelessly in performing technical assistance in many areas of this investigation.

We are indebted to Dr. Alfred M. Sellers, Dr. David W. Parsons, Dr. Julius A. Mackie, and the residents and interns on the Medical and Surgical services of the Hospital of the University of Pennsylvania, for their invaluable assistance in helping to evaluate patients before and after operation, and in insuring the best medical and surgical care for them.

BIBLIOGRAPHY

1. Wolferth, C. C., Jeffers, W. A., Lukens, F. D. W., Zintel, H. A., and Hafkenschiel, J. H.: Observations on the results of subtotal adrenalectomy in the treatment of severe, otherwise intractable hypertension and their bearing on the mechanism by which hypertension is maintained, Ann. Int. Med. **35**: 8, 1951.
2. Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H., Hills, A. G., Sellers, A. M., and Wolferth, C. C.: The clinical course, following adrenal resection and sympathectomy, of 82 patients with severe hypertension, Ann. Int. Med. **39**: 254, 1953.
3. Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H., Hills, A. G., Sellers, A. M., and Wolferth, C. C.: Evaluation of adrenal resection and sympathectomy in ninety-nine persons with hypertension, J. A. M. A. **153**: 1502, 1953.
4. Thorn, G. W., Harrison, J. H., Merrill, J. P., Criscitiello, M. G., Frawley, T. F., and Finkenstaedt, J. T.: Clinical studies in bilateral complete adrenalectomy in patients with severe hypertensive vascular disease, Ann. Int. Med. **37**: 972, 1952.
5. Bowers, R. F.: Bilateral adrenalectomy for severe hypertension, J. A. M. A. **154**: 394, 1954.
6. Smithwick, R. H., and Thompson, J. E.: Splanchnicectomy for essential hypertension, J. A. M. A. **152**: 1501, 1953.
7. Evelyn, K. A., Alexander, F., and Cooper, S. R.: Effect of sympathectomy on blood pressure in hypertension, J. A. M. A. **140**: 592, 1949.
8. Hafkenschiel, J. H., Friedland, C. K., and Zintel, H. A.: The blood flow and oxygen consumption of the brain in patients with essential hypertension before and after adrenalectomy, J. Clin. Investigation **33**: 57, 1954.
9. Hills, A. G., Venning, E. H., Dohan, F. C., Webster, G. D., and Richardson, E. M.: Pregnancy and adrenocortical function. Endocrine studies of pregnancy occurring in two adrenal-deficient women, J. Clin. Investigation, to be published.
10. Hills, A. G., Chalmers, T. M., Webster, G. D. and Rosenthal, O.: Adrenal cortical regulation of the distribution of water and electrolytes in the human body, J. Clin. Investigation **32**: 1236, 1953.
11. Hills, A. G., Webster, G. D., Rosenthal, O., Dohan, F. C., Richardson, E. M., Zintel, H. A., and Jeffers, W. A.: Quantitative evaluation of primary adrenal cortical deficiency in man, Am. J. Med. **16**: 328, 1954.
12. Grimson, K. S., Orgain, E. S., Anderson, B., and D'Angelo, G. J.: Total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy for hypertension, Ann. Surg. **138**: 532, 1953.

ULCERATIVE COLITIS: THERAPEUTIC EFFECTS OF CORTICOTROPIN (ACTH) AND CORTISONE IN 120 PATIENTS * †

By Joseph B. Kirsner, M.D., Ph.D., F.A.C.P., and Walter L. Palmer, M.D., Ph.D., F.A.C.P., *Chicago, Illinois*

Introduction

The effects of corticotropin (ACTH) and cortisone in ulcerative colitis have been characterized as beneficial,[1-5] indifferent [6-8] and unfavorable.[9-14] Numerous studies also have emphasized the complications of therapy and the recurrences.[15-20] The observation of 40 patients in 1951 [1] indicated that, while ACTH and cortisone do not cure ulcerative colitis, they may be useful adjuncts, initiating rapid and occasionally dramatic clinical improvement. The present report summarizes our experience with corticotropin and cortisone in 120 patients with ulcerative colitis observed during the past four years.

Patients Studied

General Data: The series includes 65 females and 55 males; the majority were between 20 and 40 years of age. The onset was acute in 41 cases, subacute in 22 and gradual in 57. Chronologically, the disease began during 1943 to 1953 in 83 cases; between 1933 and 1943 in 30, and between 1916 and 1933 in seven; there was no significant seasonal trend. The circumstances at the onset of the illness were not recalled by most patients; many previously had been in excellent health. At least 26 emphasized emotional problems. Nineteen patients described "intestinal infections" or "food poisoning"; an example of this group was the abrupt occurrence of cramping abdominal pain, diarrhea and fever in both father and son several hours after each had eaten hamburgers from the same food stand at a fair; the father's symptoms subsided within 48 hours; the son, also subject to recurrent rheumatic fever and rheumatic heart disease, henceforth was incapacitated by ulcerative colitis. Eighteen patients emphasized respiratory illnesses. Other events associated chronologically with the onset of ulcerative colitis were pregnancy, hay fever, physical fatigue and operations. Approximately 15 patients had been severely constipated; at

* Received for publication February 23, 1954. (Presented at Midwest Regional Meeting, American College of Physicians, Milwaukee, Wisconsin, November 21, 1953.)

From the Department of Medicine, University of Chicago.

† This study was supported in part by the Wallach Fund for Gastrointestinal Research. Dr. David Klein, of Wilson Laboratories, Chicago, Illinois, very generously supplied much of the corticotropin (ACTH).

Merck and Company provided a portion of the cortisone.

least five had been treated for irritable colon. Six patients gave an authentic family history of ulcerative colitis.

Associated Diseases: Hay fever and asthma were present in 19 cases; a family history of hay fever and asthma was elicited in 13. Eight patients had experienced rheumatic fever. Other concurrent illnesses included diabetes mellitus in four patients, hyperthyroidism in one and cirrhosis of the liver in three. Hepatic function was normal in the 26 additional patients tested. Ulcer deformity of the duodenal bulb was demonstrated in four of the 41 patients examined radiologically; the incidence of 10 per cent approximates that of a recent survey [24] and is comparable to the known frequency of peptic ulcer in the general population.

Severity of Ulcerative Colitis—Complications: The disease was classified as mild in six, moderately severe in 52 and severe in 62 of the 120 patients. The duration of symptoms at the time of this study was less

TABLE I
Extent of Ulcerative Colitis
(Radiologic)

Disease	Mild	Moderate	Severe	Totals
X-Ray Extent				
Normal	6	11		17
Rectosigmoid, descending colon		12	2	14
Including transverse colon		5	5	10
Segmental		4	1	5
Entire colon		17	44	61
Enterocolitis		1	8	9
Undetermined		2	2	4
Totals	6	52	62	120

(Terminal ileum involved in 20 patients.)

than one year in 20 cases, one to five years in 43, five to 10 years in 26, and exceeded 10 years in 31. Multiple hospitalizations had been necessary in 105 patients; 23 had been hospitalized six to 15 times. The total number of hospital days for individual cases exceeded 100 in 48 patients, 200 in 19, and ranged from 471 to 718 days in four cases.

The colon was examined radiologically in 116 patients (table 1). The entire large bowel was diseased in 61; varying portions of the colon were affected in 38 individuals; in 17 the findings were normal; many of this group had not been reëxamined for several years. Moderately severe or severe ulcerative colitis was demonstrable proctoscopically in 105 of the 120 cases (table 2); the 15 with normal mucosa or minimal abnormalities had either segmental colitis or enterocolitis.

Complications were noted in 82 of the series (table 3); multiple complications in the same patient were common.

Emotional Problems: Emotional disturbances were recognized in 105 of the 120 cases. They were classified arbitrarily as mild in 25, moderate

TABLE II

Severity of Ulcerative Colitis
(Proctoscopic)

Disease	Mild	Moderate	Severe	Totals
Proctoscopic Findings				
*Normal			3	3
*Mild	2	6	4	12
Moderate	4	25	17	46
Severe		21	38	59
Totals	6	52	62	120

* Segmental or enterocolitis.

in 34, pronounced in 28 and unusually severe in eight cases. Thirty-one patients had been interviewed by psychiatrists.

Previous Laboratory Studies: The feces consistently were negative for pathogenic bacteria and parasites. X-rays of the chest were normal. In small groups of cases the following procedures also were negative: skin tests for lymphopathia venereum, histoplasmosis and coccidioidomycosis, serum agglutinins against enteric pathogens, oral glucose tolerance test, serum calcium and phosphorus, basal metabolism, gastric secretion and tests for "L.E. cells."

Previous Treatment: Nutritional supplements, sedatives and antispasmodics had been prescribed almost routinely. Dibuline, Banthine, Prantal and Pamine were given occasionally, with variable success. Blood transfusions had been necessary in 60 patients. Sulfonamides had been administered in 107, antibiotics in 90, antiamebic drugs in 30 and vaccines in 17 cases. Small amounts of ACTH and cortisone had been given irregularly in 32 cases, with inconclusive or erratic results. The following preparations also had had no significant or sustained beneficial effect: paregoric, deodorized tincture of opium, liver extract, antihistaminics, fever therapy, "medicated"

TABLE III

Ulcerative Colitis: Complications Prior to ACTH-Cortisone Therapy
(82 Patients)

Type	No. Patients
Bleeding, anemia	48
Arthritis	35
Polyps	25
Hypoproteinemia	22
Rectal fistula	11
Thrombophlebitis	10
Rectal stricture	6
Erythema nodosum	5
Severe hemorrhoids	4
Electrolyte imbalance	3
Iritis—iridocyclitis	3
Perforation of bowel	2
Pyoderma	2
Ureteral calculus	2
Amyloidosis, adrenal insufficiency	1

enemas, extracts of hog's stomach and intestines, salicylates, bismuth, hydrochloric acid, Serutan, Kaomagma, Metamucil, mucin, thyroid extract, Lugol's solution, propylthiouracil, insulin, apples and applesauce. Five patients had required partial resection of the small bowel or sidetracking operations for regional enteritis; in four the ulcerative colitis had developed subsequently. At least 40 patients had received elsewhere the recommendation of colectomy and ileostomy.

Method of Study

The method of study has been described.[1] All patients had been under careful supervision and their previous course was known. Few had responded consistently or significantly to medical management; improvement, when it occurred, was temporary. The original 40 patients received ACTH or cortisone and occasionally sedatives. Treatment in the next 80 cases, and subsequently in all patients, included a bland diet, sedatives, antispasmodics and sulfonamides (usually sulfaguanidine, 8.0 gm. daily) alone or with penicillin and streptomycin; azulfidine was given occasionally.[22] All patients were treated in the hospital. Wilson's corticotropin and Merck's cortisone were the steroids prescribed most frequently. The initial dose for ACTH was 30 units intramuscularly every six hours (120 units daily); and for cortisone, 200 or 300 mg. orally; subsequent reductions were determined by the individual response and were made gradually to avoid abrupt changes in adrenocortical function; occasionally the dose of ACTH was increased temporarily to 160 units daily. ACTH was the dominant therapy in 108 patients; 39 of this group also received cortisone at different times. Cortisone was the only steroid administered in 12 cases (tables 4, 5). Single courses were prescribed in 65 patients (ACTH, 56; cortisone, 9); multiple courses were necessary in 55 cases (ACTH, 11; cortisone, 3; and both, 41 patients).

Table IV

Total Duration ACTH-Cortisone Therapy for Individual Ulcerative Colitis Patients

Time (Months)	ACTH	Cortisone
< 1	43	18
1–2	29	9
2–4	15	9
4–8	14	6
8–12	2	4
12–24	5	4
Totals	108	51*

* 12 patients receiving cortisone only; and 39 patients also given ACTH at different times.

In addition to the usual clinical observations, proctoscopy was repeated at intervals of seven to 14 days. The colon in 34 patients was reëxamined by x-ray at intervals up to two years after therapy. The effects of ACTH

TABLE V

Total Quantities of ACTH or Cortisone per Individual Patient

ACTH		Cortisone	
Amt. (1,000 units)	Patients	Amt. (1,000 mg.)	Patients
< 1	4	< 1	4
1–3	42	1–3	16
3–5	23	3–5	10
5–8	15	5–8	5
8–15	17	8–15	6
15–30	5	15–30	7
30–45+	2	30–40	1
		90–100	2
Totals	108	Totals	51

upon erythrocyte and serum cholinesterase, fecal nitrogen and lysozyme and upon urinary nitrogen and pepsinogen in the initial 40 cases of the series have been summarized previously.[1] Laboratory tests in the present study were limited chiefly to eosinophil counts, sedimentation rate, blood and urine glucose, leukocyte counts and the serum electrolytes.

IMMEDIATE RESULTS

The clinical response to corticotropin was estimated as good in 70 patients, moderately favorable in 24, slight in seven and nil in three; there were four deaths (table 6); thus, 94 of the 108 ACTH-patients improved significantly during treatment. The beneficial effect was characterized by

TABLE VI

Ulcerative Colitis: Clinical Response During Therapy

Response	ACTH	Cortisone
Good	70	5
Moderate	24	4
Slight	7	2
None	3	1
Deaths	4	
Totals	108	12

the prompt disappearance of fever, tachycardia, abdominal distress and bloody diarrhea, increased appetite and a pronounced sense of well-being. "Constipation" for three to five days was common; several patients had no bowel movements for two to four weeks, despite the ingestion of more than 3,000 calories daily. The response to cortisone was good or moderately favorable in nine of the 12 patients, but the clinical effects were less striking. The advantages of cortisone were fewer side effects and easier administration by mouth. The appetite increased appreciably in 108 of the 120 patients; the renewed interest in food contrasted sharply with the poor appetite preceding steroid therapy, and intakes often exceeded 4,000 calories daily. A feeling of well-being was described by 83 patients (table 7); 23 were euphoric; the re-administration of ACTH in many of this group

later failed to elicit the same emotional upsurge. The mood of 24 patients apparently did not change. Preëxisting anxiety or depression increased in 13 cases, and in several of this group culminated in psychotic episodes; the ACTH-precipitated psychosis was especially severe in one instance. Alkalosis and hypokalemia were associated with the emotional disturbances only occasionally. One patient, despite moderate clinical improvement, committed suicide; the serum electrolytes had been normal. Another patient treated subsequently also committed suicide; the two deaths by this means compare with two suicides in a group of 116 patients with benign gastric ulcer not receiving steroids. The psychogenic disturbances otherwise subsided at variable intervals after the steroids were discontinued. Emotional

TABLE VII

Certain General Effects of ACTH-Cortisone Therapy

Type		ACTH	Cortisone
Appetite	Increased	98	10
	Unchanged	10	2
Emotional State	Well-being	77	6
	No change	18	6
	Enhanced anxiety or depression	13	
	Euphoria	23	
	Insomnia	29	

problems apparently interfered with clinical progress in 31 patients; 22 of this group, nevertheless, responded to ACTH and cortisone.

The appearance of the bowel improved significantly in the majority of the patients reëxamined proctoscopically (table 8). As reported previously,[1] the earliest signs of improvement were disappearance of the excessive fluid from the rectal ampulla and subsidence of the mucosal edema; these changes usually were apparent within several days of treatment. The bleeding decreased more slowly, often persisting for periods of up to six weeks. Reversibility to a normal or near-normal mucosa was infrequent; the characteristic granularity usually persisted despite pronounced clinical improvement. Polyps and rectal strictures, when present, did not change demonstrably.

TABLE VIII

Influence of Therapy upon Rectal Mucosa in Ulcerative Colitis

Improvement	ACTH	Cortisone
Good	46	2
Moderate	33	4
None or minimal	15	1
Not examined	14	5
Totals	108	12

Among the 34 patients reëxamined radiologically, the x-rays were considered unchanged in 26. In eight cases haustrations reappeared or increased and marginal serration disappeared; however, the changes usually were slight. M.S. (unit no. 424667), with severe ulcerative colitis and giant ulcerations of the transverse, descending and sigmoid colon, responded dramatically to 2,250 mg. of corticotropin intramuscularly in 37 days, the ulcerations disappearing completely; symptoms recurred temporarily after two years of excellent health. Giant ulceration of the colon as a complication of therapy was not observed, possibly because the roentgen examinations were not repeated during treatment. The radiologic appearance of severe ulcerative colitis usually does not improve until after very prolonged remission of symptoms; hence, the x-ray method generally is not appropriate for evaluating the effects of steroid therapy in this disease.

The increased temperature and pulse rate in 45 patients returned to normal promptly, often within 24 to 48 hours. Eosinophil counts diminished in 67 of the 72 patients examined. However, the relationship was not always direct or proportionate. Whereas the counts initially reflected the degree of adrenocortical stimulation and thus provided an index of initial dosage requirements, subsequent values did not necessarily coincide with the clinical course; thus, improvement continued despite rising eosinophil counts, and several individuals did not respond despite pronounced eosinopenia. In at least six patients the eosinopenic effect decreased during the prolonged or repeated administration of ACTH.

Complications: Alkalosis developed in 76 of the 102 patients whose serum electrolytes were measured repeatedly. The chemical disturbance was severe in seven cases; an elevated serum CO_2 was the most consistent change. Hypokalemia was noted in 23 patients and was pronounced in two patients following profuse diuresis induced by mercurial diuretics. Potassium chloride by mouth increased the abdominal distress and diarrhea in five of the 10 patients so treated; hence, potassium salts were not prescribed routinely. The electrolyte imbalance usually caused weakness, headache, vertigo and nausea; however, two patients with serum CO_2 values exceeding 40 mM/L. were free of symptoms. The alkalosis subsided uneventfully when steroid therapy terminated. Hyperglycemia developed in eight of the 43 patients examined and usually was mild. Glycosuria was noted in 25 of 99 cases. Leukocyte counts rose temporarily in 62 of 92 patients; the values exceeded 15,000 in 21 cases and 20,000 in eight.

Edema occurred in 102 patients, rounding of the face in 81, acne in 69 and hypertension in 35. Other side effects were: flatulence in 38, "withdrawal" syndrome in 16, headaches in six, and vertigo and tinnitus in two; three with diabetes temporarily required more insulin. Eight patients apparently developed allergy to ACTH, with urticaria as the principal manifestation; other symptoms included generalized pruritus, erythema and extremely severe headache and tinnitus. Skin reactions were positive to both the Wilson and Armour preparations in the five cases tested.

Infections complicated therapy in 16 cases; they included furunculosis and pyoderma in five, upper respiratory illness in three, pneumonia in two, perianal abscesses and urinary infections each in two persons, and reactivation of rheumatic fever and septicemia with *Pseudomonas aeruginosa* in single cases. A young woman with severe rheumatoid arthritis, ulcerative colitis and chronic pneumonitis, after the oral intake of approximately 90 gm. of cortisone in two years, moderate amounts of phenylbutazone and huge quantities of salicylates, developed a duodenal ulcer with massive hemorrhage, requiring ligation of the bleeding artery and gastric resection.

Among the 13 patients not benefited immediately by steroid therapy, nine failures could be attributed, in part at least, to severe emotional difficulties. Seven of this group later improved during medical treatment without ACTH; one responded to larger doses of corticotropin; the ninth patient underwent total colectomy and ileostomy. Among the remaining four failures, two responded to larger amounts of ACTH and cortisone, respectively, and two required total colectomy and ileostomy.

Course after ACTH and Cortisone

The period of observation after ACTH and cortisone is less than 12 months in 45 patients and exceeds three years in 10 (table 9). Treatment subsequently has consisted of a bland, nutritious diet, rest, sedation, antispasmodics, sulfonamides and supportive psychotherapy. Among the 94

Table IX

Ulcerative Colitis: Duration Observation after ACTH, Cortisone

Months	ACTH	Cortisone
<12	37	8
12–24	26	3
24–36	32	
36–42	9	1
Totals	108	12

patients initially responding to ACTH, 68 have experienced recurrences. Symptoms also returned in six of the nine cortisone-treated cases improving immediately (table 10). Emotional tension, physical fatigue, respiratory infections, other intercurrent illness and dietary indiscretions usually were associated chronologically with the return of symptoms. Many of the re-

Table X

Recurrences after Therapy

Interval (Months)	ACTH	Cortisone
< 3	34	2
3–12	16	3
12–24	14	1
24–36	4	
Totals	68	6

TABLE XI

Severity of Recurrences

Severity	Patients
Minimal	38
Moderate	18
Severe	18
Totals	74

currences were less severe than previous attacks (table 11) and subsided with careful medical management, especially rest (table 12); many actually were relapses, occurring soon after the conclusion of treatment and suggesting premature termination of therapy.

TABLE XII

Course of Recurrences

Outcome	Patients
(a) Subsided without ACTH or cortisone	28
(b) Subsided or improving with ACTH or cortisone	22
(c) Continuing	17
(d) Requiring surgery	7
Totals	74

Remissions have continued thus far in 26 of the 94 ACTH-treated cases, and in three of the nine cortisone patients responding initially (table 13). Among the 29 patients of this group, the colitis had been mild in three, moderately severe in 15 and severe in 11 cases. Nine patients have remained well for two and three years after steroid therapy. Numerous additional cases, experiencing a recurrence shortly after treatment, subsequently have maintained satisfactory or excellent health for long periods.

TABLE XIII

Ulcerative Colitis: No Recurrences after ACTH, Cortisone

Duration Observation (Months)	ACTH	Cortisone
< 6	9	2
6–12	2	1
2–24	6	
24–36	8	
36+	1	
Totals	26	3

LONG-ACTING AND INTRAVENOUS CORTICOTROPIN, COMPOUND F, CORTISONE

Longer-acting ACTH (Wilson, Armour) in 24 cases generally was less potent than the aqueous preparation. Beneficial results were observed occasionally, as in E. R. (unit no. 541883), with extensive ulcerative colitis and radiologically demonstrable large ulcerations of the bowel. The ad-

ministration of 1,760 I.U. of longer-acting ACTH in 14 days induced pronounced improvement; the rectal mucosa later appeared normal. Corticotropin gel (Wilson), in daily intramuscular doses of 80 I.U., controlled symptoms adequately in several patients with a minimum of injections.

Corticotropin intravenously, 20 units in 500 ml. of 5 per cent dextrose in distilled water, once or twice in 24 hours, induced maximal adrenocortical stimulation. The clinical improvement in 14 patients not responding adequately to ACTH intramuscularly was striking. This type of therapy, after periods of several days to one week, was replaced by corticotropin intramuscularly.

Compound F * (hydrocortisone) was administered orally to three patients with severe ulcerative colitis. B. C. (unit no. 228631) previously had improved during ACTH therapy but on two occasions had developed severe alkalosis after the injection of 560 and 2,510 mg.; recurrent symptoms were unaffected by 610 mg. of Compound F in five days. J. V. (unit no. 144936) had responded dramatically to 376 mg. corticotropin intravenously and 1,100 mg. intramuscularly in 38 days, with a remission of 14 months' duration; severe rheumatoid arthritis and ulcerative colitis recurred despite several additional courses of ACTH and cortisone; 3,560 mg. of Compound F in 29 days induced moderate improvement. The response was much less than that produced by ACTH; fever, bloody diarrhea and arthritis returned 24 hours after the termination of therapy. C. P. (unit no. 453099) had maintained excellent health for several years during treatment with sedatives and sulfaguanidine. Recurrent symptoms subsided during the administration of 4,755 mg. Compound F in 64 days; the remission terminated after five months; hydrocortisone again seems to have controlled symptoms effectively. The observation of more patients receiving larger amounts of Compound F seems desirable in view of these preliminary findings; such a study is in progress.

Both corticotropin and cortisone were administered at different times to 39 of the 120 patients. Cortisone was prescribed usually to maintain the improvement induced by ACTH, and occasionally for the relief of relatively mild symptoms. Corticotropin excelled cortisone in 34 of the 39 cases; cortisone was superior in two instances; the clinical effects were approximately similar in three patients. These effects probably reflect quantitative rather than qualitative differences; larger amounts of cortisone might be as effective as ACTH.

Present Status

The current clinical status seems to be excellent in 35 patients and moderately improved in 57; 12 are unimproved but continue medical treatment (table 14). Nine patients underwent surgery, with excellent to satisfactory results in seven (table 15); one patient requires cortisone continuously for the control of adrenal insufficiency caused by amyloidosis.

* Kindly provided by the Upjohn Co., Kalamazoo, Michigan.

TABLE XIV

Ulcerative Colitis: Present Evaluation of Entire Group

Status	Patients
Excellent	35
Improved	57
Unimproved—medical treatment	12
Unimproved—surgical treatment	9
Dead	7
Totals	120

TABLE XV

Surgical Treatment after ACTH-Cortisone
(Nine Patients)

Procedure	Patient	Indication	Outcome
Total colectomy-ileostomy (1 stage)	P. C.	Fulminating course, massive hemorrhage	Excellent
	P. K.	Fulminating-life-saving	Moderately favorable (amyloidosis, adrenal insufficiency)
	B. N.	Frequent recurrences—decreasing response to medical treatment	Excellent
	A. S.	Fulminating course—massive hemorrhage	Good
	H. S.	Medical treatment ineffective	Excellent
Total colectomy-ileostomy (2 stages)	F. B.	Recurrent iridocyclitis	Good except for blindness
	I. S.	Frequent recurrences arthritis	Excellent
	M. S.	Recurrent—decreasing response to medical treatment	Satisfactory (persistent difficulty with ileostomy)
Partial colectomy-ileostomy (elsewhere)	H. B.	Frequent recurrences—polyposis with hemorrhage	Dead (2 yrs. later—electrolyte imbalance)

TABLE XVI

Deaths during or after ACTH Therapy in Ulcerative Colitis

Patient	Cause
B. G.	Peritonitis, retrocecal abscess (antedating ACTH)
R. G.	*Ps. aeruginosa* septicemia, pneumonia
N. M.	Fulminating colitis; shock; coma, renal failure (no autopsy)
W. P.	Hemolytic anemia (6 months after ACTH)
C. R.	Suicide
*H. B.	Electrolyte imbalance (38 months after ACTH, 2 yrs. after colectomy-ileostomy)
*M. F.	Chickenpox, pulmonary complications (20 months after ACTH)

* Deaths elsewhere.

ANALYSIS OF DEATHS

There were seven deaths (table 16). At least four of the fatalities do not appear attributable to steroid therapy. B. G. (unit no. 494107) had been hospitalized with a perforation of the cecum and abscess formation

antedating ACTH, and died of generalized peritonitis; in retrospect, surgical treatment should have been employed. W. P. (unit no. 459196), at the age of 10, had developed rheumatic fever and rheumatic heart disease; subsequently, he experienced recurrent streptococcal pharyngitis, pneumonitis, ulcerative colitis, hepatitis and progressive increase in the serum globulin to 7.6 mg. per cent. The ulcerative colitis subsided temporarily after approximately 3,000 I.U. of corticotropin in 30 days. The patient died of hemolytic anemia six months later. H. B. (unit no. 489203), two years after temporary improvement during treatment with 1,500 I.U. ACTH intramuscularly, had undergone partial colectomy and ileostomy elsewhere; he died 38 months later apparently as a result of an uncorrected electrolyte and fluid imbalance. The fourth patient, M. F. (unit no. 528795), 20 months after an excellent response to 2,290 I.U. of corticotropin in 19 days, developed severe chickenpox and died of pulmonary complications.

Three of the seven deaths may be attributed to corticotropin. N. M. (unit no. 532241) had entered the hospital critically ill and had responded to 215 units of ACTH intravenously; he suddenly developed shock, coma, renal failure and jaundice and died within several days; an autopsy was not obtained. C. R. (unit no. 514805) with severe ulcerative colitis had improved during the administration of 2,000 units of ACTH; he unaccountably committed suicide on the twenty-second day of treatment. R. G. (unit no. 211243), a debilitated woman of 69, had required partial resection of the small bowel for regional enteritis and subsequently had developed severe enterocolitis. Corticotropin, 1,920 units in 22 days, induced moderate clinical improvement. However, the patient suddenly developed weakness and fever, then coma and shock, unresponsive to plasma, parenteral fluids, penicillin and streptomycin. Physical examination and chest x-rays revealed bilateral bronchopneumonia. The serum electrolytes were normal. The final clinical episode suggested staphylococcic enterotoxic colitis, but antemortem and postmortem blood cultures revealed *Pseudomonas aeruginosa*.

Comment

The favorable clinical response in 103 of the 120 patients demonstrates the immediate beneficial effects of ACTH and cortisone in ulcerative colitis. The results are noteworthy because of the severity of the disease and the apparently small likelihood of reversibility of the colon to normal.[28] The control observations and the ineffectiveness of placebos presumably exclude psychotherapeutic factors in the response. The emotional impact of ACTH and cortisone may have contributed to the results; however, the sense of well-being generated by the steroids usually appeared to accompany or follow the clinical improvement rather than precede it. Though the emotional upsurge gradually subsided during continued treatment, the symptomatic response usually was maintained.

The clinical response to ACTH and cortisone did not differ demonstrably from the improvement observed in the absence of the steroids; however, it was more frequent and more rapid in its development. The subsidence of abdominal discomfort, rectal tenesmus and bloody diarrhea and the improvement in the proctoscopic appearance of the bowel were especially impressive. An important aspect was the encouragement given to these chronically ill patients, many of whom had lost hope of complete recovery; the reversibility of the clinical course, albeit temporary, often secured the coöperation of the patients for the prolonged medical program so necessary in this disease.

The optimal dosage requirements of ACTH and cortisone varied widely, probably depending upon the severity of the colitis, the emotional problems, fluctuations in the potency of the hormones and unexplained individual differences. The quantities of ACTH and cortisone were larger and the duration of therapy was longer in this series than in other reported studies. Thus, the total intake of corticotropin exceeded 5,000 units in 39 of 108 cases; the total intake of cortisone surpassed 5 gm. in 21 of 51 cases (12 treated with cortisone only, and 39 receiving cortisone and ACTH at different times). Corticotropin intravenously, as was to be expected, stimulated adrenocortical function most profoundly and controlled symptoms most completely and rapidly. The potencies of the other compounds investigated were, in decreasing order, aqueous corticotropin intramuscularly, longer-acting corticotropin gel intramuscularly, Compound F orally, and cortisone orally. The differences between these preparations and the routes of administration undoubtedly reflect variations in adrenocortical stimulation and in the quantities of steroids released thereby, rather than significant qualitative properties. Cortisone, though less potent than ACTH, nevertheless was highly effective in the prolonged treatment of several cases. Corticotropin gel (Wilson), in contrast to earlier preparations, also appeared to be very useful in initial daily doses of 80 I.U. once or twice daily.

In at least six cases the clinical response and the eosinopenic effect decreased steadily during the prolonged intramuscular injection of corticotropin. However, corticotropin intravenously controlled symptoms effectively in all instances, albeit temporarily. Increasing unresponsiveness to the prolonged or repeated intramuscular injection of ACTH has been observed also by other investigators.[24] The cause of this apparently refractory state is not known. The decreasing clinical response may be attributed to increasing severity of the disease. The continued potency of corticotropin intravenously would seem to exclude circulating antihormones or antibodies, though such antibodies have been demonstrated in animals [25] and in man.[26, 27] A third possibility may be fixation of corticotropin at the site of injection, with delayed diffusion into the blood stream or local inactivation of the hormone.

Despite the large quantities of ACTH and cortisone, complications fortunately were relatively uncommon and, with few exceptions, were not

serious. The "side effects" inherent in the physiologic activity of the hormones—edema, rounding of the face, acne and hypertension—developed with the usual frequency. Alkalosis and hypokalemia subsided uneventfully when the quantity of ACTH or cortisone was reduced. Peptic ulcer developed in one patient who repeatedly refused the recommendation of colectomy; she had received phenylbutazone and also, during a period of two years, more than 90 gm. of cortisone orally and enormous quantities of salicylates, at times approximating 300 gm. each month. In contrast, peptic ulcer did not develop in another patient receiving larger amounts of cortisone; and four patients with roentgenologically demonstrable duodenal ulcer experienced no untoward effects during or after the use of ACTH and cortisone. The ulcer perhaps should be attributed not only to the cortisone but also to the phenylbutazone and the salicylates. Phenylbutazone occasionally may increase gastric secretion and cause gastric or duodenal ulceration.[28] Acetylsalicylic acid in average or moderate amounts apparently does not stimulate the output of hydrochloric acid; however, large quantities may increase gastric secretion.[29] Adrenal hemorrhage was not encountered; this complication is not necessarily attributable to the adrenal steroids, for it occurs in the absence of such therapy.[30] Giant ulceration, perforation of the bowel and hemorrhage also did not occur in this series, possibly because of the large amounts of sulfonamides and penicillin and streptomycin administered concurrently.[31] In the nine patients treated by colectomy and ileostomy, the ulcerations grossly and microscopically were not larger, deeper or more numerous than the ulcerations observed in the pre-ACTH era. In one patient, giant ulcerations of the bowel, demonstrable radiologically before the use of corticotropin, disappeared after its administration. Giant ulceration of the colon is not rare in ulcerative colitis in the absence of steroid therapy,[32] and perforation with peritonitis has been a common cause of death prior to ACTH and cortisone.[33]

Corticotropin and cortisone, though immediately beneficial, do not cure ulcerative colitis. Thus far, symptoms have recurred in approximately two thirds of the series, under circumstances similar to those prevailing in the absence of steroid therapy. Perhaps, with the passage of time, symptoms will recur in all cases. The multiple courses of treatment in 55 patients and the need for surgery in nine (some of whom had responded initially) further emphasize the temporary effects of the steroids. Prolonged treatment with corticotropin and cortisone, as adjuncts to conventional therapy, may decrease the number of recurrences. Thus, the continuous administration of small amounts of cortisone and ACTH for six to 12 months has maintained the prolonged remission of ulcerative colitis in 12 patients. Complications have not developed in this group; nevertheless, intermittent stimulation of the adrenals with brief courses of ACTH probably is desirable in those patients receiving cortisone, to prevent atrophy of the adrenals and adrenal insufficiency.[34] Blanco [35] has reported excellent results with

ACTH and cortisone in "early" ulcerative colitis. The treatment of patients with relatively slight anatomic involvement and correspondingly greater potentiality for reversibility to normal may provide more favorable prospects for prolonged remissions.

Among 100 selected patients with severe ulcerative colitis studied in 1948, 81 were treated medically and 19 surgically.[26] Of the 81 medical patients, six experienced very prolonged remissions, 47 improved significantly and 19 only slightly; nine patients died (11 per cent of the medical group). Of the 19 surgically treated patients, five died. In the present series of 120 patients, medical management controlled symptoms effectively in 77 per cent of cases; 10 per cent have not improved significantly but continue therapy; 7 per cent required surgery, and the mortality rate approximated 6 per cent. The two series are not entirely comparable; nevertheless, the differences are pronounced. The more favorable course in the current group may be attributable, partially at least, to the adjunct use of ACTH and cortisone; improved medical and surgical treatment also is an important factor.

The nature of the remissions induced by corticotropin and cortisone in ulcerative colitis remains obscure. Nonspecific factors, including temporary decrease in the tissue reaction to inflammation, alterations in vascular permeability and perhaps in antigen-antibody relationships, may be implicated. Specific mechanisms may exist but they have not been demonstrated. The similar beneficial effects of ACTH and cortisone in bronchial asthma, rheumatoid arthritis and other types of "cellular hypersensitivity" attributed to antigen-antibody combinations and in ulcerative colitis have suggested a relationship between these entities. The identification of ulcerative colitis with the so-called diseases of connective tissue, suggested in earlier papers,[1, 27] remains an interesting but unproved hypothesis and is undergoing further study. Despite these and other unsolved fundamental problems in ulcerative colitis,[28, 29] the clinical evidence to date indicates that ACTH and cortisone, though potentially hazardous hormonal agents, may be useful adjuncts when administered under carefully controlled conditions. These compounds do not cure ulcerative colitis, prevent recurrences, or replace established methods of treatment. They tend rather to halt unfavorable progression of the disease, increase the rate of recovery and generally facilitate therapy, thus providing, as it were, another opportunity for careful medical treatment. Perhaps the most significant contribution of ACTH and cortisone to ulcerative colitis has been the demonstration of the potential reversibility of this complex disease, thereby stimulating further inquiry into its pathogenesis and renewing hope for its ultimate control.

Summary

Corticotropin (ACTH) or cortisone was administered to 120 patients with moderately severe or severe ulcerative colitis. The initial doses were, for ACTH, 30 I.U. intramuscularly every six hours (120 units per day);

and for cortisone, 200 or 300 mg. by mouth daily. The immediate clinical response to corticotropin was judged as good or favorable in 94 of the 108 ACTH patients, and in nine of the 12 cortisone patients. The response included the prompt subsidence of fever, tachycardia, abdominal distress and bloody diarrhea, and increased appetite and a pronounced sense of well-being. The proctoscopic appearance of the bowel improved in the vast majority of this group. Eosinophil counts decreased significantly in 67 of the 72 patients examined. Alkalosis occurred in 76 of the 102 patients whose electrolytes were measured repeatedly; hyperglycemia in eight of 43 patients; glycosuria in 25 of 99 patients, and leukocytosis in 62 of 92 patients. Edema developed temporarily in 102 patients, rounding of the face in 81, acne in 69 and hypertension in 35. Eight patients developed allergy to ACTH. Infections complicated therapy in 16 instances.

Symptoms have recurred thus far in 68 of the 94 patients responding initially to ACTH, and in six of the nine cortisone-treated cases improving immediately. Many of the recurrences appeared to be less severe than those preceding steroid therapy and have subsided with careful medical management; some of these recurrences were, in fact, relapses, occurring soon after the termination of therapy.

Remissions have continued in 26 of the 94 patients in the ACTH group and in three of the nine in the cortisone group responding immediately; nine patients have remained well two and three years after treatment. Numerous additional patients, experiencing recurrences shortly after treatment, subsequently have remained well for long periods. Corticotropin gel, through less potent than the aqueous preparation, was clinically effective in occasional patients. Corticotropin intravenously induced striking and, at times, dramatic improvement in the 14 patients not responding adequately to ACTH intramuscularly. Compound F, administered orally in moderate amounts to three patients, appeared to be less effective than ACTH and more potent than cortisone.

The current clinical status seems excellent in 35 patients and moderately improved in 57; 12 are unimproved, but continue medical treatment; nine patients required colectomy and ileostomy, with excellent to satisfactory results in seven. There were seven deaths, four of causes unrelated to steroid therapy and three probably attributable to the use of corticotropin. In the entire series of 120 patients, medical treatment controlled symptoms effectively in 77 per cent; 10 per cent were unimproved but continue therapy; 7 per cent required surgery, and 6 per cent died.

Conclusion

Corticotropin (ACTH) and cortisone do not specifically cure ulcerative colitis, prevent recurrences or replace established methods of treatment; nevertheless, when administered in sufficient quantities and with due regard

for the various complications of steroid therapy as well as of the disease itself, the hormones are useful therapeutic adjuncts.

BIBLIOGRAPHY

1. (a) Kirsner, J. B., Palmer, W. L., and Klotz, A. P.: ACTH and cortisone in chronic ulcerative colitis. A comparison of clinical effects, J. Lab. and Clin. Med. **36**: 846, 1950.
   (b) Kirsner, J. B., and Palmer, W. L.: ACTH in ulcerative colitis. Report of progress, Gastroenterology **18**: 143, 1951.
   (c) Kirsner, J. B.: Discussion of "ACTH in chronic ulcerative colitis," Proc. Second Clinical ACTH Conference, 1951, The Blakiston Co., Philadelphia, p. 500.
   (d) Kirsner, J. B., and Palmer, W. L.: Effect of corticotropin (ACTH) in chronic ulcerative colitis. Observations in forty patients, J. A. M. A. **147**: 541, 1951.
2. McKell, T. E., Tuthill, S. W., and Sullivan, A. J.: The affective response of a patient with chronic ulcerative colitis to cortisone, Gastroenterology **17**: 20, 1951.
3. (a) Gray, S. J., Reifenstein, R. W., Benson, J. A., Jr., and Young, J. C. G.: Treatment of ulcerative colitis and regional enteritis with ACTH, Arch. Int. Med. **87**: 646, 1951.
   (b) Gray, S. J., Reifenstein, R. W., Benson, J. A., Jr., and Young, J. C. G.: Treatment of ulcerative colitis with corticotropin (ACTH) and cortisone, J. A. M. A. **148**: 1489, 1952.
4. Machella, T. E., and Hollan, O. R.: The effect of cortisone on the clinical course of chronic regional enteritis and idiopathic ulcerative colitis, Am. J. M. Sc. **221**: 501, 1951.
5. (a) Wirts, C. W., and Carroll, J. L.: The use of ACTH in the treatment of ulcerative colitis, Rev. Gastroenterol. **19**: 13, 1952.
   (b) Wirts, C. W., Rehfuss, M. E., and Yantes, H. A.: Long-term results in corticotropin-treated ulcerative colitis, J. A. M. A. **154**: 36, 1954.
   (c) Brown, G. M., and McAuley, J. S.: Cortisone therapy in ulcerative colitis, J. A. M. A. **150**: 1587, 1952.
6. (a) Elliott, J. M., Kiefer, E., and Hurxthal, L. M.: ACTH in the treatment of chronic ulcerative colitis, Gastroenterology **19**: 722, 1951.
   (b) Kiefer, E. D., and Elliott, J. M.: The effect of ACTH therapy upon the course of chronic ulcerative colitis, Gastroenterology **26**: 29, 1954.
7. Halsted, J. A., Adams, W. S., Sloan, S., Walter, R. L., and Bassett, S. H.: Clinical effects of ACTH in ulcerative colitis, Gastroenterology **19**: 698, 1951.
8. Flood, C. A., and Lepore, M. S.: Medical management of chronic ulcerative colitis, New York State J. Med. **52**: 2265, 1952.
9. Dearing, W. H., and Brown, P. W.: Experiences with cortisone and ACTH in chronic ulcerative colitis, Proc. Staff Meet., Mayo Clin. **25**: 486, 1950.
10. Rosmiller, H. R., Brown, C. H., and Ecker, J. A.: The effect of ACTH on non-specific ulcerative colitis, Gastroenterology **17**: 25, 1951.
11. Redish, M. H.: Failure of cortisone in chronic ulcerative colitis disease of the large and small bowel, Gastroenterology **18**: 179, 1951.
12. Crohn, B. E., and Yarnis, H.: Present trends in the treatment of ulcerative colitis, New York State J. Med. **51**: 2129, 1951.
13. McHardy, G., Bechtold, J. E., and Browne, D. C.: Therapeutic advances in gastroenterology. II. (a) The antibiotics. (b) Corticotropin and cortisone, Louisiana State M. J. **105**: 147, 1953.
14. Bercovitz, Z. T.: A long-range evaluation of modern methods in the treatment of chronic ulcerative colitis, New York State J. Med. **53**: 2200, 1953.

15. Tulin, M., Kern, F., Jr., and Almy, T. P.: Perforation of bowel during treatment of ulcerative colitis with corticotropin. Report of three cases, J. A. M. A. **150**: 559, 1952.
16. Texter, E. C., Jr., Legerton, C. W., Ruffin, J. M., Boyd, J. A., Jr., and Smith, A. G.: Idiopathic ulcerative colitis: giant ulceration following corticotropin (ACTH) and cortisone therapy, Arch. Int. Med. **91**: 744, 1953.
17. Pessel, J. F., Bearisto, E. B., Edwards, M. H., Rothwell, T. K., and Wise, J. S.: Multiple perforations occurring during the treatment of ulcerative colitis with ACTH, Am. J. Digest. Dis. **20**: 322, 1953.
18. Sauer, W. G., Dearing, W. H., and Wollaeger, E. E.: Serious untoward gastrointestinal manifestations possibly related to administration of cortisone and corticotropin, Proc. Staff Meet., Mayo Clin. **28**: 641, 1953.
19. Larkin, M. A., and Flannery, M. G.: Surgical experience with corticotropin in ulcerative colitis, Arch. Surg. **66**: 386, 1953.
20. Wilson, D. A. W., and Roth, D.: Adrenal apoplexy occurring during corticotropin therapy of ulcerative colitis, J. A. M. A. **152**: 230, 1953.
21. Halsted, J. A., Yuhl, E. T., Stirrett, L. A., and Barker, W. R.: The association of peptic ulcer with chronic ulcerative colitis, Gastroenterology **26**: 65, 1954.
22. (a) Svartz, N.: The pathogenesis and treatment of ulcerative colitis, Acta med. Scandinav. **141**: 172, 1951.
(b) Svartz, N.: The treatment of ulcerative colitis, Gastroenterology **26**: 26, 1954.
(c) Bargen, J. A.: Treatment of ulcerative colitis with salicylazosulfapyridine (Salazopyrine), M. Clin. North America **33**: 935 (July) 1949.
23. Kirsner, J. B., Palmer, W. L., and Klotz, A. P.: Reversibility in ulcerative colitis, Radiology **57**: 1, 1951.
24. Renold, A. E., Jenkins, D., Forsham, P. H., and Thorn, G. W.: The use of intravenous ACTH, a study in quantitative adrenocortical stimulation, J. Clin. Endocrinol. and Metabolism **12**: 763, 1952.
25. Gordon, G. L.: The development of a refractory state to adrenocorticotropic hormone, Endocrinology **45**: 471, 1949.
26. Brown, E. M., and Hollander, J. L.: Allergy to ACTH and the use of beef ACTH, Proc. Second ACTH Conference (1950), J. R. Mote, Editor, 1951, The Blakiston Co., Philadelphia, Vol. 2, p. 392.
27. Feinberg, S. M., Feinberg, A. R., and Bigg, E.: Allergy to pituitary corticotropic hormone, J. A. M. A. **147**: 40, 1951.
28. Kirsner, J. B.: Unpublished observations.
29. Clark, B. B., and Adams, W. L.: The effect of acetylsalicylic acid on gastric secretion, Gastroenterology **9**: 461, 1947.
30. (a) Berte, S. J.: Spontaneous adrenal hemorrhage in the adult. Literature review and report of two cases, Ann. Int. Med. **38**: 28, 1953.
(b) Greene, R. C.: Spontaneous idiopathic adrenal apoplexy associated with hypertension, J. A. M. A. **152**: 133, 1953.
31. Jawetz, E., and Merrill, E. R.: The effect of cortisone upon the therapeutic efficacy of antibiotics, Science **118**: 549, 1953.
32. (a) Sulzberger, F. M.: Acute ulcerative colitis. Report of case, New England J. Med. **233**: 87, 1945.
(b) Jobb, E., and Finkelstein, A.: Interesting x-ray findings in a case of acute fulminating ulcerative colitis, Gastroenterology **8**: 213, 1947.
(c) Griffiths, L. L., and Gilchrist, L.: Fatal case of acute ulcerative colitis with multiple perforations, Brit. M. J. **1**: 1366, 1951.
(d) McEwen, K. L., and Lodwell, E. A.: Acute fulminating idiopathic ulcerative colitis, Radiology **59**: 185, 1952.

33. Jankelson, I. R., McClure, C. W., and Sweetsir, F.: Idiopathic ulcerative colitis. Perforation of the bowel, Rev. Gastroenterol. **12**: 31, 1945.
34. Salassa, R. M., Keating, F. R., Jr., and Sprague, R. G.: Clinical aspects of suppression of adrenal cortical function after use of cortisone, Proc. Staff Meet., Mayo Clin. **28**: 662, 1953.
35. Blanco, H. G.: Considerations on the pathogenesis of ulcerative colitis: its treatment with ACTH and cortisone, Ap. de la des. Clinica No. 3–15, 1953.
36. Kirsner, J. B., Palmer, W. L., Maimon, S. N., and Ricketts, W. E.: Clinical course of chronic non-specific ulcerative colitis, J. A. M. A. **137**: 922, 1948.
37. Levine, M., Kirsner, J. B., and Klotz, A. P.: A new concept of the pathogenesis of ulcerative colitis, Science **144**: 552, 1951.
38. Machella, T. E.: Problems in ulcerative colitis, Am. J. Med. **13**: 760, 1952.
39. Kirsner, J. B., and Palmer, W. L.: Ulcerative colitis: consideration of its etiology and treatment, J. A. M. A. **155**: 341, 1954.

ATYPICAL TUBERCULOSIS OF THE LIVER WITH JAUNDICE *

By EDWARD A. CLEVE, Colonel, MC, F.A.C.P., JOHN R. GIBSON, Major, MC, and WILLIAM M. WEBB, Lieutenant Colonel, MC, F.A.C.P.,
San Francisco, California

TUBERCULOSIS of the liver with jaundice is rare.[1-6] Four cases will be presented with the results of streptomycin therapy.

Tuberculosis of the liver, excluding miliary tuberculosis, has been variously described as "primary," [7, 8] "conglomerate tuberculosis and tuberculous cholangitis," [9] "tuberculomata," [10] "tuberculous hepatitis," [11] "tubular tuberculosis," [12] "disseminated caseating" [6] and "focal." [12] "Atypical abdominal tuberculosis," proposed by Blair and Pagel,[13] is an excellent term to designate unusual tuberculous involvement of abdominal organs and structures. "Atypical tuberculosis of the liver" is used by us where the liver is principally or exclusively involved in the tuberculous infection and where there are signs and/or symptoms of the hepatic involvement.

Warthin [14] reported a well defined icterus in 80 per cent of his cases of acute general miliary tuberculosis of the typhoid form and in a similar percentage of cases of chronic tuberculosis ending in general miliary metastasis. However, this observation has not been confirmed. Cruice [15] found only a single case of mild jaundice caused by miliary tuberculosis of the liver in 570 autopsies performed upon patients dying of chronic pulmonary tuberculosis, and but seven cases of jaundice in 1,748 cases of tuberculosis. It has been estimated [12] that miliary tubercles in the liver are found in more than 50 per cent of all autopsies on tuberculous patients, usually without clinical manifestations of hepatic involvement. By contrast, when tuberculosis has exclusively or principally involved the liver, the hepatic signs and symptoms have frequently been the most prominent manifestations in the patient. In most instances the tuberculosis remained unsuspected prior to laparotomy or postmortem examination.

CASE REPORTS †

Case 1. A 28 year old Filipino male soldier was hospitalized for four months in 1945 with jaundice, dark urine, anorexia and epigastric distress. On bed-rest and dietary therapy his icterus disappeared, and he was returned to duty asymptomatic. Thereafter, he was apparently well until January, 1949, when he came under the care of one of us (E. A. C.) and was hospitalized. Jaundice, dark urine and epigastric distress had recurred about 10 days previously and had been accompanied

* Received for publication January 4, 1954.
From the Letterman Army Hospital, San Francisco, California.
† All cases were hospitalized at the U. S. Philippine Scout Hospital, Manila, P. I. Cases 1 and 2 were observed by the senior author (E. A. C.). Cases 3 and 4 were observed by Major Francisco Roque, who is presently stationed at Fitzsimons Army Hospital, Denver, Colorado.

by light, loose stools and afternoon fever. The epigastric pain was almost constantly present and unrelated to food ingestion. During the previous year a 20 pound weight loss had occurred.

Physical Examination: Height, 61 inches; weight, 100 pounds; temperature, 100° F.; pulse, 92; blood pressure, 112/76 mm. of Hg. Marked icterus of the skin and sclerae was present, with several spider angiomata on the chest. The liver was enlarged below the right costal margin to the level of the umbilicus and had a firm, nontender edge. The spleen was questionably palpable. No other abnormalities were noted.

Laboratory Data: Chest roentgenogram on admission revealed in the right apex fibrocalcific densities 1 cm. in diameter which remained stabilized throughout hospitalization. Second strength PPD was positive, 2 plus. Serologic test for syphilis, repeated blood cultures, an upper gastrointestinal series and a cholecystogram were negative or within normal limits. Hookworm and ascaris ova, for which the

TABLE I

Liver Function Studies in Case 1

Date	Serum Bilirubin, Mg./100 c.c.	Thymol Turbidity, Units	Cholesterol Mg./100 c.c.	Chol. Esters, Mg./100 c.c.	Alkaline Phosphatase, Bodansky units
1-11-49	8.6	10.9	437		55
1-24-49	7.6	9.5	217		96.4
2-10-49	6.0	10.8	680	264	113
2-24-49	6.75	9.9	364	150	60.4
3-4-49	7.2	10.0	309		105
3-23-49	Exploratory Laparotomy				
3-30-49	Streptomycin Begun				
4-7-49	5.7	7.3			
4-18-49	2.8	5.8			64.8
5-11-49	1.6	1.8	335	146	26.2
6-21-49		1.4			7.0
7-12-49		1.8	322	165	9.0
8-2-49		3.0			15.1
8-4-49	Streptomycin Discontinued				
9-13-49		7.7	267		16.0
12-13-49	0.48	3.6	242	126	7.2
1-24-50	0.37	2.7	210		10.2
4-18-50	0.5	2.9			

patient was treated with hexylresorcinol and tetrachloroethylene, were noted on stool examination. Red blood count varied from 3.3 to 4.7 million; hemoglobin, 9.4 to 15.2 gm.; white blood count, 6,600 to 12,700, with 45 to 74 per cent neutrophils, 20 to 40 per cent lymphocytes, 0 to 4 per cent monocytes, and 0 to 20 per cent eosinophils. Total serum proteins were 7.3 gm. per 100 c.c., of which albumin was 4.37 gm. and globulin 2.93 gm., with little variation subsequently. Significant tests of hepatic function are summarized in table 1.

Course: The patient received a diet high in protein, calories and vitamins. During the first three months his symptoms and physical findings remained essentially unchanged, but there was an almost daily fever of one to four degrees, with marked diurnal variation. On March 23, 1949, under spinal anesthesia, an exploratory laparotomy was performed. The liver extended to the umbilicus, with a collapsed gall-bladder and a normal common bile duct. On the under surface of the liver there were numerous firm yellow nodules measuring 0.5 to 1 cm. in diameter. A 3 by 3 cm. lymph node was located immediately to the right of the common bile duct and superior to the duodenum. The remainder of the abdomen was explored

with no positive findings. The operative diagnosis was metastatic malignant tumor with primary site undetermined. The lymph node was excised and several of the hepatic lesions were biopsied. Pathologically, all specimens were composed of dense fibrous tissue consisting of conglomerate tubercles of whirled connective tissue with caseation necrosis and surrounding lymphocytes, epithelioid cells, monocytes and scattered Langhans' giant cells. In the sections taken from the liver there were, in addition, scattered dilated and tortuous bile ducts. Acid-fast bacilli typical of *M. tuberculosis* were present in all sections. The immediate postoperative course was uneventful. The patient was treated with 1 gm. of streptomycin daily from March 30 through August 4, for a total dose of 127 gm. Within three weeks of the initiation of this therapy the patient was afebrile and remained so throughout hospitalization. Symptomatic improvement was striking and was manifested by an increased appetite, a sense of well being, and a weight gain of 18 pounds. Hepatomegaly progressively receded, and by July 18, 1949, neither the liver nor the spleen could be palpated. A dramatic improvement in the liver function studies paralleled the clinical changes. When last seen, on July 31, 1950, one year after the completion of streptomycin therapy, the patient was asymptomatic and apparently well.

Case 2. A 23 year old male Filipino was hospitalized March 20, 1949, with right upper lobe pulmonary infiltrations discovered on routine chest roentgenogram prior to separation from the military service. On admission he denied cough, hemoptysis, chills, fever, chest pain or night sweats. In January, 1948, a mild anorexia and a definite scleral icterus had appeared and had persisted to the time of admission. A moderate weight loss had occurred during this 14 month period. There had been no abdominal pain or distress. The color of the urine and of the stools had not been noted.

Physical Examination: Height, 64 inches; weight, 109 pounds; temperature, 100° F. The patient appeared chronically ill. There was moderate icterus of the skin and sclerae. The liver was enlarged to the level of the umbilicus, and the spleen extended one fingerbreadth below the left costal margin. There was no lymphadenopathy, and the lungs were clear.

Laboratory Data: On admission the red blood count was 4.5 million; hemoglobin, 15.2 gm.; white blood count, 6,000, with 56 per cent neutrophils, 37 per cent lymphocytes and 6 per cent eosinophils. The sedimentation rate was 11 mm. per hour (Wintrobe). Stool examinations revealed hookworm and Trichuris ova, for which the patient was treated with tetrachloroethylene. Urinalysis, nine gastric cultures for acid-fast bacilli, and serologic test for syphilis were negative or within normal limits. Chest roentgenograms revealed in the upper lobe of the right lung hazy, nodular densities which did not change subsequently. First strength PPD was positive, 2 plus. Icterus index was 40 units on March 20, increased to a maximum of 100 units on July 27, and subsequently fell gradually to within normal limits by December. Thymol turbidity rose from an initial level of 4.5 units to a peak value of 49.5 units in September and later returned to normal. Total cholesterol on admission was 234 mg. per 100 c.c., and reached a maximum of 1,320 mg. per 100 c.c. (704 mg. esters per 100 c.c.) in September. Subsequently it returned to normal. Alkaline phosphatase rose from an initial level of 22 units (Bodansky) in April to a peak of 126 units in July and subsequently returned to normal in November. Prothrombin time varied from 70 to 80 per cent of normal during the first several months of hospitalization and later returned to within normal limits. Total serum proteins on June 30, 1949, were 6.24 gm. per 100 c.c., with albumin 3.38 gm. and globulin 2.86 gm.

Course: During the first two months of hospitalization low-grade fever, anorexia and hepatomegaly persisted. On June 14, 1949, a slight swelling was first noted in

the right parotid region. By August 3, the mass extended from the angle of the right jaw to the zygomatic process, and 20 c.c. of a sanguinopurulent fluid were aspirated from it. No organisms were seen on smear of this material, and it was sterile on routine culture as well as on guinea pig inoculation for acid-fast bacilli. The mass subsequently disappeared. Roentgenograms of the hands were negative. On August 5, 1949, an exploratory laparotomy was performed. The spleen and the liver were moderately enlarged, and on the surface of the latter were seen several firm, white or yellow nodules varying in size from 0.5 to 1 cm. A large, firm mass was present in the region of the head of the pancreas. The gall-bladder was distended and could not be emptied. Fungating, subserosal masses 1 to 4 cm. in diameter were present on the antimesenteric border of the ileum. The appendix was stony hard. Microscopic examination of the biopsy specimens removed from the head of the pancreas, one of the subserosal lesions of the ileum, and the meso-appendix revealed granulomatous inflammation characterized by the formation of tubercles. The predominant cellular components were epithelioid cells and numerous giant cells of both the Langhans and foreign body types. Caseation necrosis and acid-fast organisms could not be demonstrated. It was the opinion of the Armed Forces Institute of Pathology that the lesion did not appear diagnostic and was not typical of either tuberculosis or sarcoidosis. Unfortunately, specimens of the hepatic lesions were not obtained at laparotomy. However, in view of the remarkable similarity to the preceding case in clinical manifestations and laboratory findings, the positive PPD, and the negative serology, a clinical diagnosis of tuberculosis was made. Streptomycin, 0.5 gm. twice a day, was given from July 9 through December 30, 1949, for a total dose of 177 gm. The patient's appetite promptly improved, and by September 1, 1949, the spleen was no longer palpable, and the liver had gradually receded in size until it was barely palpable. Diminishing icterus paralleled the symptomatic improvement. In August, 1949, diabetes mellitus was diagnosed on the basis of compatible symptomatology, glycosuria, and typical blood sugar determinations. A rapid and progressive 31 pound weight gain followed control of the diabetes by dietary therapy and protamine zinc insulin. By December, 1949, the patient was afebrile and asymptomatic, icterus had disappeared, and tests of liver function were normal. On a 2,000 calorie diet and protamine zinc insulin he remained entirely asymptomatic and apparently well through August, 1950, eight months after completion of streptomycin therapy, when he was last seen following separation from the military service.

Case 3. A 28 year old Filipino male was hospitalized April 22, 1947, with complaints of a chronic cough productive of abundant greenish white sputum without hemoptysis, recent slight weight loss, and aching pain in the knees.

Positive findings on physical examination were slight enlargement and tenderness of the left anterior and posterior cervical lymph nodes, scattered coarse râles over the lower lobe of the left lung, enlargement of the liver to three fingerbreadths below the right costal margin with a sharp and nontender edge, a spleen palpable 1 cm. below the left costal margin, and heat, tenderness and limitation of motion involving the right knee and both wrist joints.

Course: The joint symptoms rapidly cleared without specific therapy and did not recur, but the liver and spleen remained palpable. Chest roentgenograms revealed a small infiltration in the apex of the right lung. This was thought to represent inactive pulmonary tuberculosis. Gastric washings and sputa examinations were repeatedly negative for acid-fast bacilli on culture and guinea pig inoculation. The hemogram and urinalysis were within normal limits on many occasions. On May 2, 1947, the total serum proteins were 7.2 gm. per 100 c.c., with an albumin/globulin ratio of 1.0. Thymol turbidity was 25 units. Irregular low grade fever was apparent shortly after admission and persisted. Icterus appeared initially in August, 1947, and became marked. During the following several months the clinical course was

characterized by persistent productive cough, weight loss, irregular low grade fever, jaundice, anorexia, hepatomegaly, splenomegaly, and tenderness in the upper right quadrant of the abdomen. An upper gastrointestinal series was within normal limits. Alkaline phosphatase was 58.8 and 51 units (Bodansky) on two occasions. Cholesterol was 363 mg. per 100 c.c. The abdomen was surgically explored in May, 1948, and a small amount of fluid was found in the peritoneal cavity. The gall-bladder and all peritoneal surfaces were studded with gray, firm nodules from 1 mm. to 1 cm. in diameter. The gall-bladder could be emptied easily, and there was no evidence of extrahepatic biliary obstruction. Biopsies taken from the omentum, sigmoid, lymph nodes, falciform ligament and liver revealed tuberculosis in all specimens. The postoperative course was relatively uneventful. Icterus gradually receded, and by June 4, 1948, the icterus index was 4 units. Cephalin cholesterol was 2 plus in 24 hours. Bromsulphalein retention was 24 per cent after 30 minutes. A moderate ascites appeared. In June, 1948, a homogeneous shadow appeared in the base and upper lobe of the left lung on a chest roentgenogram. Streptomycin, 0.25 gm. four times a day, was administered from June 17 through July 26, 1948, for a total dose of 40 gm. Shortly after streptomycin was begun the ascites disappeared, and the patient became afebrile and symptomatically improved. On July 23 he complained of moderate diffuse abdominal pain. About 15 minutes later he had five generalized convulsions and never regained consciousness. Cerebrospinal fluid was normal except for a protein content of 151 mg. per 100 c.c. He died July 26, 1948.

Postmortem Examination: There were widespread tuberculous lesions involving the pleura, lungs (active and healed disseminated tuberculosis, minimal), peritoneum, celiac, periportal, mesenteric and pancreatic lymph nodes, and ileum. The liver weighed 1,600 gm. and had a smooth and glistening capsule with a few 2 mm. gray nodules. A moderate periportal cirrhosis was present. The intrahepatic bile ducts were dilated up to 2 cm. in diameter throughout both lobes and were filled with inspissated clumps of firm, greenish black material. The walls were thickened and fibrotic. Microscopically, there was a uniform increase in fibrous tissue in the periportal areas with bile duct proliferation. Sections including the larger bile ducts revealed dark yellow material in dilated lumina with the epithelium replaced by fibroblasts and mononuclear cells. Numerous fibrocaseous tubercles were seen around the ducts and extending along the periportal areas. Sections of brain revealed in the basal ganglia several foci of ring hemorrhages around small arterioles occluded by thrombi with parenchymal destruction and surrounding areas of edema.

Case 4. A 34 year old Filipino male developed jaundice and epigastric distress unrelated to food ingestion in September, 1946. He was initially hospitalized in November, 1946, but was discharged one month later with persistent jaundice. Records of this hospitalization were not available. Jaundice and epigastric distress persisted until his second hospital admission, in January, 1948. On February 17, 1948, a cholecystostomy was performed. At the time of operation the liver was enlarged and its surface studded with numerous small white fibrous nodules. A small specimen of liver surgically excised was lost prior to pathologic examination. The surgical wound in the upper right quadrant of the abdomen did not completely heal, and a small draining sinus persisted. Epigastric distress remained unchanged following cholecystostomy. A gradual progressive weight loss ensued over the following months. In May, 1948, chest roentgenogram was normal, and icterus index was 26.6 units. A normocytic anemia with hemoglobin of 11 to 12 gm. per 100 c.c. persisted. The white blood and differential counts remained within normal limits. In July, 1948, total cholesterol was 162 mg. per 100 c.c. In October chest roentgenogram revealed no abnormalities except elevation of the dome of the right diaphragm. In November, 1948, examination of the biliary system after the injection of an opaque

medium through the fistulous opening in the right hypochondrium showed the fistulous tract to be apparently connected with the cystic duct. The common bile duct was enlarged, as were some of the hepatic ducts, which were bulbous in shape. There was no evidence of obstruction. Afternoon fever to a maximum of 101° F. appeared in September, 1948, and persisted throughout the remainder of hospitalization. In February, 1949, serum bilirubin was 1.8 mg. per 100 c.c. at one minute, 5.6 mg. at 30 minutes. Thymol turbidity was 8.8 units. Total serum proteins were 7.9 gm. per 100 c.c., with albumin 4.3 gm. and globulin 3.6 gm. Prothrombin time was normal. On April 2, 1949, icterus index was 117 units. On April 5 an exploratory laparotomy was performed. The biliary fistulous tract from the gall-bladder to the skin was excised. The liver was enlarged, and its surface was studded with many small white fibrous nodules. The peritoneum and omentum were gray and thickened. Specimens of representative tissues were excised. On microscopic examination the fistulous tract revealed a large central area of caseous necrosis with surrounding fibrous tissue in which there were prominent infiltrations of lymphocytes, plasma cells, epithelioid cells and Langhans' giant cells. Acid-fast bacilli were present. The liver tissue was replaced largely by tubercles of fibrous tissue, hyaline or caseous substance. The liver cells were granular and indistinct. Many acid-fast bacilli were seen. Streptomycin, 0.5 gm. twice a day, was given from April 21 through May 5, 1949, when the patient left the hospital against advice to enter a local charity hospital. His subsequent course is unknown. When last seen on May 5, 1949, he was icteric and had slight afternoon fever.

Discussion

Cases 1, 3 and 4 represented hepatic tuberculosis in view of the typical histologic findings and the presence of acid-fast organisms in the tissues. Cultural confirmation was not attempted. Case 2 was considered tuberculosis from the clinical and therapeutic standpoints. Sarcoidosis was strongly considered, particularly in view of the right parotid gland involvement, but confirmatory evidence in support of this diagnosis could not be established.

The elevation of the serum alkaline phosphatase (to 113 units in case 1, 126 units in case 2, and 58 units in case 3) and the hypercholesterolemia (680 mg. per 100 c.c. in case 1, 1320 mg. in case 2, and 363 mg. in case 3) are worthy of comment. In cases 1 and 3 there was no evidence of extrahepatic biliary obstruction, and the etiology of the hypercholesterolemia and hyperphosphatemia is obscure. In a review of the literature in the English language of atypical tuberculosis of the liver, including 25 patients with jaundice, we were unable to find a single case with similar laboratory abnormalities. Guild and Robson [16] reported a case of tuberculous splenomegaly with hepatomegaly, but without proved tuberculous involvement of the liver, in which the icterus index was 15 units and the alkaline phosphatase 21.5 units (King). The prolonged icterus, hypercholesterolemia and hyperphosphatemia without evidence of extrahepatic biliary obstruction are suggestive of cholangiolitic hepatitis as described by Watson and Hoffbauer.[17]

In case 2 the hypercholesterolemia and hyperphosphatemia may be attributed in part to extrahepatic biliary obstruction caused by the large mass in the region of the head of the pancreas. At laparotomy the gall-bladder was distended and could not be emptied. Jaundice caused by tuberculous

extrahepatic biliary obstruction has been described on several occasions. Hodenpyl [18] reported an unusual case in which the clinical course lasted but seven days and was marked by abdominal pain, fever and increasing jaundice. At autopsy the common bile duct was occluded by a mass of enlarged tuberculous lymph nodes. In a review of the literature of extrahepatic causes of jaundice in tuberculosis, Cruice [15] found several cases where the cause was apparently enlarged tuberculous lymph nodes pressing upon the bile ducts. In one such instance jaundice had been present for two years. In our patient jaundice had been present by history for 14 months prior to hospital admission and persisted an additional seven months, subsiding finally following streptomycin therapy.

Most writers have stressed the difficulty of making an accurate diagnosis of tuberculosis of the liver prior to histologic examination of the involved tissues. Particularly is this true if there is no evidence of tuberculosis elsewhere in the body. Even a negative Mantoux and repeated punch biopsies of the liver revealing normal hepatic tissue do not exclude the diagnosis, as exemplified by the case described by Choremis and Ninios,[11] in which the diagnosis was finally established by histologic examination of liver tissue obtained at laparotomy.

Analysis of our cases of atypical tuberculosis of the liver with jaundice and similar cases from the literature revealed fever, chills, hepatomegaly and abdominal pain or distress to be the most common manifestations.

Jaundice has been of variable degree but most often mild or moderate. Cruice [15] believed that the degree of jaundice was helpful in surmising the pathologic condition, intense jaundice probably being due either to pressure of tuberculous glands on the extrahepatic bile ducts or to some form of the solitary tubercles of the liver, milder forms being produced by a miliary tuberculosis of the liver. It is doubtful if such a pathologic differentiation can be made on the basis of the degree of icterus. Rather, in 25 cases in the literature and in our four cases there has been an inconstant relationship between the degree of icterus and the underlying hepatic pathology. The jaundice, once established, has more often been constant than intermittent, although usually of variable degree, but in at least two instances [7, 19] the icterus has occurred in distinct episodes.

Hepatomegaly of variable degree has been present in most cases. Ashton's case [10] was unique in that large, soft, nodular masses could be readily palpated on the liver surface. Splenomegaly has been associated not infrequently.

Abdominal pain in the epigastrium or upper right quadrant, of variable character and severity and unrelated to food ingestion, has been noted frequently but has not been characteristic or diagnostic. Biliary colic has not, to our knowledge, been described.

Fever, usually low grade, with or without chills, has been almost universally present, but because of its extreme variability, even in a single patient, has not been of appreciable differential diagnostic significance.

Even in the presence of characteristic features such as hepatomegaly, fever, chills and abdominal pain, atypical tuberculosis of the liver with jaundice must in most instances remain a pathologic diagnosis. If the disease has persisted for several months, or if there is evidence of tuberculosis elsewhere in the body, the possibility of a tuberculous etiology is enhanced. A discharging fistula on the abdominal wall following laparotomy, as noted in our case 4 and in one of Neill's cases,[9] should always suggest the possibility of tuberculosis. At laparotomy the true nature of the process has rarely been appreciated, and metastatic malignancy has been the most common operative diagnosis.

Treatment

A definitive diagnosis in tuberculosis of the liver can no longer be considered of purely academic interest. With the advent of the newer antibiotics and chemotherapeutic agents, the dictum of Morris [20] that "a fatal termination may be expected in tuberculosis of the liver" is apparently no longer valid. Several examples of satisfactory results following streptomycin therapy in hepatic tuberculosis have now been reported. Choremis and Ninios [11] in 1948 treated a 14 year old male with 45 gm. of streptomycin over a period of two months with clinical improvement. He was discharged as "clinically cured" and his condition remained "normal" during a five month subsequent period of observation. Melville [21] reported a satisfactory result in a case of hepatic tuberculosis with jaundice treated with 107 gm. of streptomycin over a three and one-half month period. Guild and Robson [16] noted a dramatic response to 81 gm. of streptomycin in a patient with tuberculous splenomegaly and miliary tuberculosis. Hepatic tuberculosis was not proved. The patient died of congestive heart failure four months after a second course of streptomycin (54 gm.). Neill's patient [9] died four days after streptomycin therapy was instituted. Meredith, Early and Becker [22] administered streptomycin to a patient with tuberculous splenomegaly who had miliary tuberculosis with microscopic hepatic tuberculosis but without macroscopic liver involvement at laparotomy or clinical evidence of hepatic disease. In spite of a good response initially to streptomycin, the patient subsequently died.

In two of our patients (cases 3 and 4) an evaluation of the efficacy of streptomycin therapy cannot be made. Case 3 died of cerebral thromboses after symptomatic improvement on therapy. Case 4 left the hospital against advice shortly after streptomycin was commenced.

The response to streptomycin in a dose of 1 gm. daily for four months (total dose, 127 gm.) in case 1 and for almost six months (total dose 177 gm.) in case 2 was favorable, and when last seen both patients had been apparently well and without clinical or laboratory evidence of intra-abdominal disease for periods of seven months and one year, respectively, following termination of streptomycin therapy.

In view of the accumulated evidence [22] that prolonged intermittent streptomycin therapy in conjunction with daily para-aminosalicylic acid or isoniazid is the treatment of choice in pulmonary tuberculosis, such a regimen would likewise seem to be indicated in tuberculosis of the liver. We feel that with early diagnosis and adequate therapy with the present antituberculosis drugs, the prognosis in atypical tuberculosis of the liver need no longer be uniformly poor.

Summary

Tuberculosis of the liver with jaundice is rare. Four cases with unusual findings are presented. The most frequent manifestations are jaundice of mild or moderate degree, low grade fever, chills, hepatomegaly and abdominal distress. In most instances the condition is not diagnosed prior to laparotomy or postmortem examination.

"Atypical tuberculosis of the liver" is proposed to designate exclusive or principal involvement of the liver by tuberculous infection where there are clinical manifestations of hepatic disease.

Several instances of satisfactory results with streptomycin therapy of tuberculosis of the liver are recorded in the literature. In two of our cases there was a dramatic response to streptomycin, and the patients were apparently well seven months and one year, respectively, after termination of streptomycin therapy.

With early diagnosis and adequate therapy with the present antituberculosis drugs, the prognosis in atypical tuberculosis of the liver need no longer be uniformly poor.

BIBLIOGRAPHY

1. Leader, S. A.: Tuberculosis of the liver and gall bladder with abscess formation, Ann. Int. Med. **37**: 594, 1952.
2. Schiff, L.: The differential diagnosis of jaundice, 1946, The Year Book Publishers, Inc., Chicago, Illinois, p. 72.
3. Bockus, H. L.: Gastro-enterology, Vol. 3, 1946, W. B. Saunders Co., Philadelphia, p. 266.
4. Mowitt, E. R.: Jaundice. Its pathogenesis and differential diagnosis, 1947, Oxford University Press, New York, p. 199.
5. Geraghty, F. J.: Jaundice in tuberculosis, Am. Rev. Tuberc. **45**: 521, 1942.
6. Thayer, W. S.: On disseminated caseating tuberculosis of the liver, Bull. Johns Hopkins Hosp. **22**: 146, 1911.
7. De Crespigny, C. T., and Cleland, J. B.: A case of primary multiple tuberculomata of the liver with a degenerated hydatid cyst, M. J. Australia **1**: 151, 1923.
8. Frank, L.: Primary tuberculosis of the liver, Am. J. M. Sc. **123**: 630, 1902.
9. Neill, D. G.: Tuberculosis of the liver: including a report of five cases, M. J. Australia **1**: 893, 1951.
10. Ashton, N.: A case of multiple tuberculomata of the liver, J. Path. and Bact. **58**: 95, 1946.
11. Choremis, C. V., and Ninios, N.: A case of tuberculous hepatitis and its biological reactions, Acta paediat. **37**: 188, 1949.

12. Rosenkranz, K., and Howard, L. D.: Tubular tuberculosis of the liver, Arch. Path. **22**: 743, 1936.
13. Blair, E. J., and Pagel, W.: Fulminant tuberculous septicemia and other atypical forms of abdominal tuberculosis, Tubercle **28**: 115, 1947.
14. Warthin, A. S.: The occurrence of icterus in tuberculosis, Internat. Clin. **1**: 89, 1911.
15. Cruice, J. M.: Jaundice in tuberculosis, Am. J. M. Sc. **147**: 720, 1914.
16. Guild, A. A., and Robson, H. N.: Polycythemia vera with tuberculous splenomegaly, Edinburgh M. J. **57**: 145, 1950.
17. Watson, C. J., and Hoffbauer, F. W.: Problem of prolonged hepatitis, Ann. Int. Med. **25**: 195, 1946.
18. Hodenpyl, E.: A case of apparent absence of the spleen, with general compensatory lymphatic hyperplasia, M. Rec. **54**: 695, 1898.
19. Winternitz, M. C.: Tuberculosis of the spleen, Arch. Int. Med. **9**: 680, 1912.
20. Morris, E.: Tuberculosis of the liver, Am. Rev. Tuberc. **22**: 585, 1930.
21. Melville, I. D.: Tuberculosis of the liver treated with streptomycin, Brit. M. J. **1**: 1187, 1951.
22. Meredith, H. C., Early, J. Q., and Becker, W.: Tuberculous splenomegaly with hypersplenism syndrome, Blood **4**: 1367, 1949.
23. Tempel, C. W., Pitts, F. W., and Dye, W. E.: Antimicrobial therapy of pulmonary tuberculosis: review of six years' experience at Fitzsimons Army Hospital, Ann. Int. Med. **39**: 61, 1953.

BUDD–CHIARI SYNDROME (OCCLUSION OF THE HEPATIC VEINS): SEVEN CASES *

By EDDY D. PALMER, Lt. Colonel, MC, F.A.C.P., *Washington, D. C.*

THE Budd-Chiari syndrome, or Chiari's syndrome, is the disease complex which follows hepatic vein occlusion. It is a moderately well popularized secondary abdominal response to several disease processes, but the number of reported cases remains remarkably small. During the past 32 months seven autopsy-proved cases and four presumptive cases have been observed. This appears to be a large experience with the syndrome, perhaps explained by the fact that a large tumor center was the source of material. From 1910 to 1939 at the Mayo Clinic 20 instances were encountered.[1] Only five were found during 11,979 autopsies at Stanford University.[2]

Lambron is said to have reported the first case, in 1842.[3] The earliest discussion of the subject, a very brief one, is that contained in the first (or 1846) edition of Budd's [3] book on liver disease, published in Philadelphia. He had noted instances of liver abscess which led to thrombosis of the hepatic veins. In 1899 Chiari [4] established for the first time a proper clinical and pathologic explanation for the syndrome. He described endophlebitis of the hepatic veins as especially significant, collecting 10 cases and describing three of his own. Hoover [5] found 30 case reports by 1920, and Kahn and Spring,[6] 60 by 1940. In 1946 the figure of Hirsh and Manchester [7] was 70, and Thompson [8] reviewed 95 recorded cases in 1947. In 1952 Little and Montgomery [9] estimated that 115 cases had been recorded.

Men appear to be a little more prone to hepatic vein occlusion than women. The average age at the time of diagnosis (usually autopsy) among 86 collected cases was stated to be 34 years.[8] The youngest reported patient was that of Gee,[10] aged 17 months.

There are many basic causes and many courses to be kept in mind when the clinical diagnosis comes under consideration. This is a syndrome which depends on vascular occlusion, and such occlusion may be sudden and complete or gradual and partial. There is a potential portal-systemic collateral venous system available, but probably a considerable interval is necessary for its functional development. No doubt the severity of the clinical manifestations depends on the ratio between the rapidity and degree of hepatic vein obstruction and the efficiency of the collateral venous channels, as Hutchison and Simpson [11] suggested; however, the mechanisms are necessarily such flexible ones that in any patient conditions must be in a constant state of flux.

* Received for publication March 3, 1954.
From the Gastroenterology Service, Walter Reed Army Hospital, Washington, D. C.

When occlusion occurs suddenly, either as the first episode or as an acute episode superimposed upon chronic partial obstruction, death may follow within a few days. The central vein of the liver lobule connects with the hepatic veins directly through the valveless sublobular veins, so that back pressure is exerted directly on the hepatic cells. There are severe right upper quadrant pain, nausea and vomiting secondary to sudden mucosal congestion, rapidly developing ascites, shock with cyanosis and uncontrollable hypotension, rapidly progressive hepatomegaly, cholemia and death.

In the more chronic case the clinical manifestations are easily understood, on the basis of the anatomic site of venous occlusion. Clinical progress is characteristically irregular, and unpredictable acute episodes may alter the degree of venous obstruction at any time. Right upper quadrant and epigastric pain is the most constant symptom and often is the first warning of trouble. There is of course hepatomegaly, plus the right upper quadrant tenderness and shock-pain which are secondary to hepatic congestion. Cirrhosis is the final stage of the liver disease, but some of the common clinical stigmata of cirrhosis may antedate the progress of the liver damage. Thus, portal hypertension and ascites are prominent early. Rapidity of accumulation is characteristic of the ascites. Depending on the degree of chronicity, serial abdominal paracenteses may be required. The fluid is hemorrhagic at times. Occasionally hydrothorax accompanies the ascites in this syndrome, as it may under other circumstances. Splenomegaly ordinarily remains of small degree. Edema of the legs may develop if there is concomitant occlusion of the inferior vena cava. If the hepatic veins are completely and chronically occluded, the venous outflow from the liver must utilize afferent channels in a retrograde fashion. The usual portal-systemic collateral vessels open, and the venous pattern over the abdomen becomes prominent. Quick death from bleeding esophageal varices may rarely eventuate. If the hepatic veins become recanalized, or if collaterals develop sufficiently, there may be recession of the effects of portal hypertension. It is particularly important to note the direction of flow in distended abdominal veins in determining possible concomitant occlusion of the inferior vena cava.

It is not unusual for Chiari's syndrome to represent the final episode in already advanced disease, which either masks the onset of the new development or proceeds too rapidly to permit the characteristic picture to appear. If cirrhosis or chronic congestive heart failure is already present, it is apparent that additional liver enlargement will be limited and that gradual obstruction of the hepatic veins may go unrecognized. The same may be true if hepatoma or Pick's disease has already been diagnosed. Thus, of the 20 cases due to thrombotic occlusion reported by Kelsey and Comfort,[1] other clinical considerations obscured or overshadowed the Chiari's syndrome in 16 patients so that the condition was not recognized until autopsy.

Jaundice requires special comment. Study of the cases reported in the

appended bibliography leads one to believe that clinical jaundice is both rare and mild in the chronic form of the syndrome. Notation of the reported circulating bilirubin levels, however, suggests that clinical icterus must have been rather prominent in several of the cases during the chronic stage.

In all cases a marked disturbance of hepatic function is evident upon laboratory study. Even during rather stable chronic phases, no esterified cholesterol may be detectable, the bromsulphalein retention may amount to 70 per cent in 45 minutes (5 mg./Kg.), the serum albumin may reach low levels, and all flocculation tests may show maximal positivity. During the final stages, of course, there is total hepatic incompetence with cholemia.

The course of the chronic form ordinarily lasts only a few months. Death usually is the result of hepatic coma. Less frequently, an associated hepatic or other malignant tumor, intercurrent infection, rupture of esophageal or gastric varices, or portal or mesenteric thrombosis with infarction of the bowel may terminate events. Hutchison and Simpson [11] had the remarkable opportunity of following a patient from onset at the age of five years to termination at 28 years, whereupon at autopsy a carcinoma of the liver was found, in addition to hepatic vein occlusion.

The liver pathology does not appear to be very complicated. The changes are entirely secondary and largely mechanical. The liver becomes enlarged by passive venous congestion, which is reflected directly to the central lobular veins. Grossly, the result is a nutmeg liver. Depending on the number of hepatic veins involved and the anatomic distribution of the tributaries of the affected veins, the congestion may be localized or generalized. Occasionally only one lobe or part of a lobe becomes obstructed. Thus Hess [12] described an instance in which tremendous hepatomegaly was found to be localized largely to the spigelian lobe. Central lobular vein distention and stasis lead to central lobular necrosis and atrophy. There often is, in addition, hemorrhage into the lobular substance. As the liver enlarges, atrophy progresses. Fibrous replacement follows. Old and recent lesions may occur side by side. The characteristic autopsy triad is venous congestion, central necrosis and fibrous replacement. The liver may present the picture of cirrhosis with nodular regenerative hyperplasia. Hepatoma is a rather frequent finding. The older concept—that syphilis is the cause of the syndrome—has been entirely dispelled by both clinical and autopsy studies, beginning with the observations of Thompson and Turnbull [13] in 1912.

Seven proved cases of Chiari's syndrome are reported here. More important, perhaps, would be presentation of cases which survived following recanalization and recovery from the effects of hepatic vein occlusion. The diagnosis in such a case would be open to enough doubt that its discussion might be misleading. It may be permissible to note, however, that four apparent instances of development of and recovery from Chiari's syndrome were observed during the period of study of the seven fatal cases. The apparent etiology or circumstance at origin of each case was: (1) altered

circulatory dynamics during resection of aortic coarctation; (2) diabetes and furunculosis; (3) sickle cell anemia, and (4) polycythemia vera. The proved cases will be outlined briefly.

Case Reports

Case 1. This 66 year old alcoholic male was hospitalized because of four months of moderate diarrhea and intermittent white stools. There had been increasing abdominal swelling for four days.

Upon examination, the patient appeared old, tired and sick, but the nutrition was apparently good and the vital signs were normal. The abdomen was tightly distended by fluid, but it was thought that moderate hepatomegaly could be demonstrated. There was moderate edema of the feet and ankles. No spider angiomata or prominent abdominal veins were found.

Hemogram, urinalysis, x-ray study of the gastrointestinal tract, sigmoidoscopy and gastroscopy were normal. Chest film showed minimal hydrothorax on the left. Serum albumin/globulin was 2.5/3.0 gm. per 100 ml. Liver function studies suggested moderate disease. The Bromsulphalein retention was 23 per cent at 45 minutes. Cytologic study of ascitic fluid revealed malignant cells. Liver biopsy showed portal cirrhosis.

The day after admission, abdominal paracentesis was necessary because of respiratory interference. Ascitic fluid re-accumulated rapidly, necessitating frequent taps. Edema progressed, and jaundice developed. The total serum bilirubin rose rapidly from 0.8 to 23 mg. Renal output suddenly failed six weeks after admission, and death followed in three days.

At autopsy deep jaundice, edema and massive ascites were evident. There was moderate bilateral hydrothorax. The right lobe of the enlarged liver (2,425 gm.) was partly replaced by a tumor measuring 20 cm. in diameter. The tumor extended by continuity through the hepatic veins and into the vena cava. The latter was blocked by a rod of tumor which extended upward into the right atrium. Both the portal and the splenic veins were blocked by tumor. Esophageal varices were present. Metastatic tumor was found in both lungs. The important histopathologic diagnoses were portal cirrhosis and primary liver-cell hepatoma.

Case 2. This 23 year old white soldier was hospitalized upon complaining of swollen glands in the neck, recognized for four weeks. Physical examination was entirely normal except for a matted cluster of enlarged nodes in the left supraclavicular fossa, which was removed easily; the pathologic diagnosis was reticulum cell sarcoma. Exhaustive studies failed to give positive evidence of tumor elsewhere, although radiologic study after retroperitoneal air insufflation was thought to suggest a mass just inferior to the left kidney. The decision was to withhold therapy until more tumor became evident or hematologic abnormality appeared.

The patient was recalled from duty four months later for follow-up examination. He had no complaints except for swelling of the feet at the end of the day and occasional night sweats. He had lost no weight. Examination showed an apparently healthy young man. There were slight pedal edema, lymphadenopathy of the left anterior cervical chain, and a small fixed midline mass deep in the hypogastrium. Peripheral blood and marrow studies were normal. All liver function studies were normal. The temperature ranged to 100° or 101° F. daily.

A course of deep radiation therapy over five midline portals from diaphragm to pubis was given during a 38 day period. There was no change in the size of the tumor, and a week following completion of radiation it was found that ascites was developing. The course was then one of rapid deterioration, to death three weeks later. Ascites accumulated rapidly, the superficial venous pattern of the abdomen suddenly became prominent, the spleen enlarged moderately, the liver descended half-

way to the umbilicus and became very tender, generalized lymphadenopathy appeared, constant back pain required heavy analgesia, anorexia and nausea were severe, there was high fever, and gross hematuria developed. Anuria rather suddenly supervened, and the patient died two days later. The day prior to death the total serum bilirubin was 3.2 mg.

At autopsy, there was reticulum cell sarcomatosis of the superficial node chains, mediastinal nodes, and most of the retroperitoneal area. The liver weighed 3,860 gm. and showed passive congestion but no tumor. A continuous tumor mass ensheathed the aorta and cava from the aortic bifurcation to the liver. The cava had been invaded by tumor just proximal to the renal veins and was partially occluded by a rod of tumor which extended into the right atrium. It appeared that the cava had been capable of transmitting about half its usual volume of blood. At the level of the caval fossa of the liver, the tumor had become applied to the anterior caval wall, where it had infiltrated into the liver, obliterating the area normally occupied by the ostia of the hepatic veins.

Case 3. A 23 year old white soldier was hospitalized because of rapid weight loss and abdominal pain. Radiologic and gastroscopic study revealed a large gastric tumor. At laparotomy the tumor was found to be unresectable, and there were liver metastases. Biopsy showed leiomyosarcoma. A course of supervoltage radiation therapy was given over the stomach area, without clinical improvement.

Two weeks after completion of radiation the patient suddenly developed ascites. At the time he had been bed-ridden for four weeks, was wasting rapidly and was

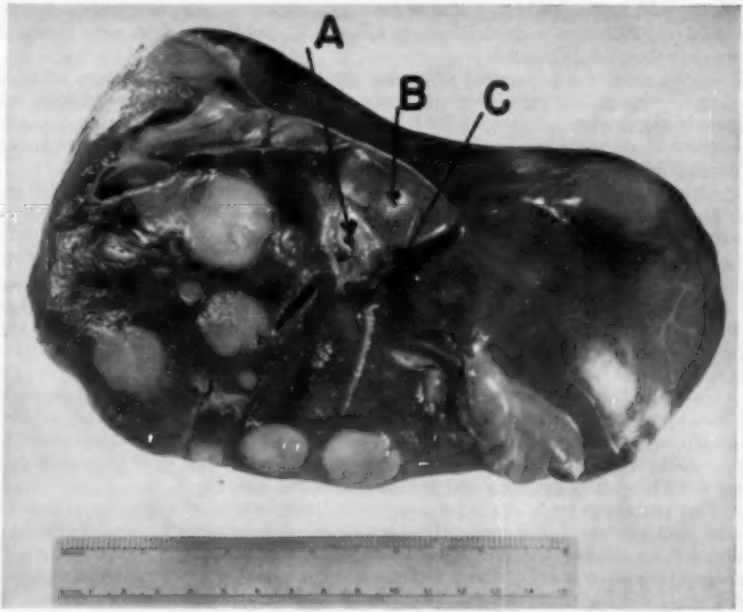


FIG. 1. *Case 3.* Inferior surface of liver. Metastatic leiomyosarcoma from stomach. A: Portal vein. B: Caudate lobe. C: Partially cut-away inferior vena cava, containing thrombi emerging from hepatic veins. The inferior surface of the left lobe of the liver has been sliced off, to expose two dilated hepatic veins. Further dissection revealed no tumor in the neighborhood of the porta hepatis.

considered to be entering the terminal few days of his illness. The ascites accumulated rapidly. A new and severe pain developed in the right flank and across the back. The liver was thought to be enlarging slowly. There was no jaundice, splenomegaly, edema or prominent abdominal veins. The patient died a week after the onset of ascites.

At autopsy primary leiomyosarcoma of the stomach was found. The liver, lungs and regional nodes were involved by large metastases. There were 3,000 ml. of clear yellow ascitic fluid. The inferior vena cava was clear, and the spleen was not enlarged. The liver weighed 2,600 gm. The ostia of the four hepatic veins (figure 1) were occluded by antemortem thrombi, which extended back into the liver for distances of from 2 to 4 cm. There was no tumor in the immediate neighborhood of the thrombi. Moderately extensive phlebothrombosis was also found in the pelvic and left femoral veins.

Case 4. Five years prior to his terminal hospitalization, this 61 year old white man sought medical help because of awkward gait, bleeding gums and abdominal mass. Appropriate studies revealed chronic myelogenous leukemia. There was no ascites or clinical evidence of portal hypertension, but, because the liver as well as the spleen was enlarged, a liver biopsy was taken and portal cirrhosis discovered. He was treated with nitrogen mustard and blood transfusions, with good clinical results. During the following five years he was hospitalized four times, receiving another course of nitrogen mustard and further transfusions each time.

Ascites, prominent abdominal veins and esophageal varices were first demonstrated two years before the final admission. These appeared consistent with the cirrhosis, which upon re-biopsy was found histopathologically to be severe. Because of rapid accumulation with respiratory difficulties, the ascitic fluid was tapped 35 times over the next 24 months.

At the time of the terminal admission the picture was that of severe advanced cirrhosis. Except for the white cell blood count of 197,000 and tremendous splenomegaly, there were no signs of the leukemia. He had no new complaints. During the course of study the patient suddenly and for the first time vomited a large amount of blood. He quickly went into liver failure and died.

At autopsy the important findings were a gray nodular liver weighing 2,250 gm., ascites, esophageal varices with demonstrable point of dissolution, and a hard leukemic spleen weighing 1,300 gm. There was no significant lymphadenopathy. The inferior vena cava was normal. Histopathologic study confirmed the diagnosis of cirrhosis and leukemia.

When the hepatic veins were searched for, it was found that they were represented by fibrous cords which were distinguished with difficulty from a fibrous mass which involved the caudate lobe, caudate process and part of the nonperitoneal surface. No veins joined the vena cava in the hepatic vein area.

Case 5. This 50 year old white man had been treated as an out- and in-patient for two years for a variety of simple complaints, and the diagnoses of portal cirrhosis, duodenal ulcer, gastric ulcer, multiple rectal adenomas and chronic alcoholism had been established. He had never been very sick, and by far the most important problems were his heavy drinking and troubles with the law.

Five months prior to death he was hospitalized because of gradually progressive ascites and edema of the legs. His long-standing hepatomegaly was found to be static, but for the first time spider angiomas, prominent abdominal venous pattern and splenomegaly were noted. There was moderate anemia, the serum albumin/globulin level was 1.7/3.5 gm. per 100 ml., liver biopsy showed advanced portal cirrhosis, and esophagoscopy revealed a normal esophagus. Abdominal paracentesis recovered 6,200 ml. of clear yellow fluid. The patient was hospitalized for one month for detailed metabolic studies, and dietary and diuretic therapy. There was no response in the ascites, and repeated abdominal taps were necessary. The serum bilirubin remained

only slightly elevated. The patient had no complaints other than the abdominal swelling and attendant dyspnea.

The final seven weeks of the patient's course were observed in the hospital. Back pain, frequent nausea, diarrhea and extreme fatigue had developed. There were now jaundice and "flapping tremor." The abdomen had to be tapped once a week. The signs of portal hypertension were striking, but repeated esophagoscopic examinations did not show varices. There were scarring and deformity of the gastric antrum at the site of the old stomach ulcer. The patient gradually became severely jaundiced and cholemic, and died quietly of liver failure.

At autopsy the important findings centered about the liver. The scarred lesser curvature of the gastric antrum and the transverse colon were adherent in a fibrous mass to the underside of the liver, the head of the pancreas and the left kidney. There was, however, no perihepatitis, hepatic abscess or active inflammation in the area. The liver weighed 1,950 gm., and was grossly nodular and obviously very fibrotic. The superior group of hepatic veins, as observed in the wall of the opened vena cava, consisted of three narrowed vessels with thick hard walls. Each was occluded by a white fibrous clot which ended flush with the caval wall and which could not be separated from the wall of the hepatic veins. When the liver substance was dissected away, it was found that the venous obliteration extended only a short way into the hepatic veins, but that there was generalized chronic endophlebitis throughout the liver. The inferior group of hepatic veins could not be found.

Case 6. This retired soldier, who "had never had a day of sickness," sought medical help at the age of 64 because of the rather sudden onset of right-sided abdominal pain and diarrhea. Upon examination it was found that he was 25 pounds below his normal weight, there was mild ascites, the liver extended 4 cm. below the right costal margin in the nipple line at rest, the spleen was palpable, there was true gynecomastia, and the abdominal venous pattern was prominent. No varices could be demonstrated by esophagoscopic examination. Stools were consistently positive for occult blood. Cirrhosis was suspected, but liver biopsy upon admission showed only chronic venous congestion. Cytologic examination of the ascitic fluid failed to reveal malignant cells. Thorough study failed to give direct proof of the basic disease process, but the working diagnosis became carcinoma of the pancreas. Gradual development of back pain, subclinical diabetes and metastatic pulmonary disease was considered adequate confirmation. The course was a rapid one, marked by cachexia and obstructive atelectasis, and the patient died four months after the onset of symptoms. There had been no appreciable progression in the degree of ascites, of hepatic enlargement or of splenomegaly. There had been no elevation of the serum bilirubin. A splenic rub was heard terminally.

At autopsy the body and tail of the pancreas were the site of tumorous replacement. There was direct extension through the wall of the stomach and duodenum. Overlying the area of the porta hepatis and encasing the aorta and vena cava there was a baseball-sized mass of carcinomatous nodes. Transverse section showed the cava to be plugged with tumor, and upon further dissection the intraluminal tumor was found to extend from the level of the pancreas to the diaphragm. The ostia of the hepatic veins had been invaded a few millimeters. The liver was large (2,790 gm.) and congested, and contained a few small metastases. The portal vein and its tributaries were patent. The spleen showed only moderate congestive enlargement. Esophageal varices could not be demonstrated. The histopathologic diagnosis was adenocarcinoma of the pancreas.

Case 7. This 78 year old Negro man had been remarkably healthy until seven months prior to the terminal hospitalization, when the complaint of hoarseness led to the discovery of carcinoma of the larynx and to laryngectomy. Shortly afterwards he developed sharp upper abdominal pain with radiation to the right flank. Anorexia became severe, and there was rapid weight loss. Examination revealed chronic wasting, normal vital signs, severe generalized arteriosclerosis, and edema of the left leg. The

liver was moderately enlarged, hard, and irregular in outline. There was no anemia or occult melena. The albumin/globulin levels were 2.2/4.7 gm., Bromsulphalein retention (5 mg./Kg.) in 45 minutes was 34 per cent, and serum bilirubin, 1.4 mg. Liver biopsy revealed anaplastic carcinoma, without suggestion of origin.

The patient lived only three weeks. The edema of the leg partly subsided, but ascites gradually became apparent. The size of the liver did not change. The superficial abdominal venous pattern could be distinguished during the final week. The serum bilirubin remained stable.

Autopsy showed primary carcinoma of the body and tail of the pancreas, with large metastases to the liver (3,570 gm.), the regional nodes and left adrenal gland. Tumor had infiltrated and replaced a large part of the posterior aspect of the liver and adjacent diaphragm. This mass had obliterated the hepatic veins by infiltration, a process which appeared to have been complete for some time. The inferior vena cava and the portal system were patent. Histopathologic study suggested that all of the tumor found was of pancreatic rather than laryngeal origin.

Comment

For the clinician's purposes, an understanding of the basic diseases which may be complicated by Chiari's syndrome is of primary importance. Under all clinical circumstances, of course, it is such a rare complication that little anticipatory value may be expected from such an understanding. Rather, the recognition of Chiari's syndrome may on occasion be helpful in elucidating obscure primary abdominal disease. This could have been so in some of the patients reported here had the significance of certain of the sudden changes in the clinical pictures been properly interpreted. In only three of the seven cases had the possibility of Chiari's syndrome been recorded in the chart before death.

Some thoughts on etiology are expressed in the table. The site of obstruction may be the inferior vena cava at the level of the caval fossa of the liver, the ostia of the hepatic veins, or within the hepatic veins themselves. One should note that obliterating thrombophlebitis of the inferior vena cava is a common accompaniment of Chiari's syndrome. Nishikawa's [14] lengthy discussion of the matter may be considered classic. On the other hand, it is important to understand that in only about 4 per cent of cases of thrombosis of the inferior vena cava does the thrombus extend superiorly into the upper one third of the vessel; [8] therefore, primary caval thrombosis is rarely complicated by Chiari's syndrome. Hepatoma and intraluminal extension of malignant tumors along the inferior vena cava have been illustrated in the present series. One might suppose that surgical decompression of portal hypertension might encourage hepatic vein thrombosis, but only one such case, that of de Almeida,[15] has been clearly reported. This patient, after an unsuccessful attempt at splenorenal shunt, was treated by splenectomy alone. No congenital basis for the syndrome has ever been proved. Several cases have been associated with polycythemia vera, although Sohval [16] found, on reviewing the experiences of others with the disease, that the hepatic veins are among the rarest localizations for spontaneous thrombosis in polycythemia.

Summary

Seven proved cases of Chiari's syndrome have been reported, the major primary diagnosis in two instances being carcinoma of the pancreas, and, in one instance each, hepatoma, reticulum cell sarcomatosis of the abdomen, leiomyosarcoma of the stomach, chronic myelogenous leukemia, and portal cirrhosis. A tabulation of the various potential etiologic circumstances is presented.

Table I

Causes, Proved and Speculative, of Chiari's Syndrome

I. Congenital
   1. Obliteration of ductus venosus extends too far? [17]
   2. Intra-uterine obliteration of venae revehentes extends too far? [11]
   3. Congenital stricture at junction of hepatic veins and vena cava? [10]
   4. Fibrosis following fetal interstitial hepatitis occludes hepatic veins or prevents their junction with vena cava? [18]
   5. Familial lipomatosis? [10]

II. Mechanical
   1. Debilitating disease or prolonged shock with deceleration of transhepatic venous flow.
   2. Trauma to hepatic region.[9]
   3. Postural torsion of hepatic veins causes scar and occlusion? [20]
   4. Secondary to Pick's disease.
   5. Result of venous anomaly, valvular fold? [8]
   6. Eddying of streams at junction of veins? [13]
   7. Repeated trauma of coughing with tearing of vein walls and thrombosis? [20]
   8. Following surgical portacaval decompression.[15]

III. Hematologic
   1. Sickle cell anemia.[7]
   2. Polycythemia vera.[2, 16, 21–27]
   3. Leukemia.[14]

IV. Diffuse Liver Disease
   1. Cirrhosis.[1, 11, 14, 21, 28]
   2. Virus hepatitis?
   3. Syphilitic hepatitis?
   4. Schistosomiasis?

V. Local Liver Disease
   1. Perihepatitis?
   2. Abscess.[1, 3]
   3. Hydatid cyst.
   4. Gumma.
   5. Hepatoma.[2]
   6. Metastatic tumor.[1, 2]
   7. Actinomycosis.[1]

VI. Acquired Vascular Disease
   1. Primary hepatic endophlebitis? [4, 12]
   2. Hepatic periphlebitis?
   3. Thrombophlebitis of inferior vena cava.[14]
   4. Hepatic endophlebitis secondary to abdominal inflammation.
   5. Simple phlebothrombosis, unexplained.
   6. The generalized vascular diseases.[29]
   7. Schistosomiasis of hepatic veins?

VII. Diseases of Neighboring and Other Organs
   1. Pancreatic cyst?
   2. Regional lymphadenopathy.
   3. Diaphragmatic tumor, gumma, fibrosis.
   4. Malignant extension within inferior vena cava.[2, 30]
   5. Subphrenic and other intraperitoneal abscess.[1]
   6. Carcinoma of gall-bladder.[1]
   7. Diffuse peritonitis leading to periphlebitis or endophlebitis.[1]
   8. Associated with pregnancy.[4]

BIBLIOGRAPHY

1. Kelsey, M. P., and Comfort, M. W.: Occlusion of the hepatic veins: review of twenty cases, Arch. Int. Med. **75**: 175–183, 1945.
2. Armstrong, C. D., and Carnes, W. H.: Obstruction of the hepatic veins (Chiari's disease): report of five cases, Am. J. M. Sc. **208**: 470–478, 1944.
3. Budd, G.: Diseases of the liver, 1846, Lea & Blanchard, Philadelphia, p. 151.
4. Chiari, H.: Über die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache, Beitr. z. path. Anat. u. z. allg. Path. **26**: 1–17, 1899.
5. Hoover, C. F.: Obstruction of hepatic veins, J. A. M. A. **74**: 1753–1756, 1920.
6. Kahn, S., and Spring, M.: Thrombosis of the hepatic veins—Chiari's syndrome: report of a case with biopsy and venous pressure determination, Ann. Int. Med. **14**: 1075–1083, 1940.
7. Hirsh, H. L., and Manchester, B.: Chiari's syndrome: report of a case, New England J. Med. **235**: 507–511, 1946.
8. Thompson, R. B.: Thrombosis of the hepatic veins; the Budd-Chiari syndrome, Arch. Int. Med. **80**: 602–615, 1947.
9. Little, R. D., and Montgomery, P. O'B.: Case report of stenosis of the vena cava with vena caval and hepatic vein thrombosis related to trauma, Ann. Int. Med. **37**: 197–203, 1952.
10. Gee, S. J.: Complete obliteration of the mouths of the hepatic veins, St. Barth. Hosp. Rep. London **7**: 144–146, 1871.
11. Hutchison, R., and Simpson, S. L.: Occlusion of the hepatic veins with cirrhosis of the liver, Arch. Dis. Childhood **5**: 167–186, 1930.
12. Hess, A. F.: Fatal obliterating endophlebitis of hepatic veins, Am. J. M. Sc. **130**: 986–1001, 1905.
13. Thompson, T., and Turnbull, H. M.: Primary occlusion of the ostia of the hepatic veins, Quart. J. Med. **5**: 277–296, 1912.
14. Nishikawa, Y.: Über die Obliteration der Stammlebervenen und des heparen Hohlvenenabschnittes (Thrombophlebitis obliterans venae hepaticae et venae cavae inferioris), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **20**: 151–305, 1918–19.
15. de Almeida, A. D.: Contribuição para o estudo da anastomose espleno-renal (com especial atenção à via de acesso), Tese, Univ. de São Paulo, p. 243, 1951.
16. Sohval, A. R.: Hepatic complications in polycythemia vera, with particular reference to thrombosis of the hepatic and portal veins and hepatic cirrhosis, Arch. Int. Med. **62**: 925–945, 1938.
17. Moore, F. C.: Primary obliterative inflammation of main trunks of hepatic veins, M. Chron. **3**: 240–251, 1902.
18. Rosenblatt, O. G.: Über einen Fall von abnormen Verlauf der Lebervenen in Verbindung mit Cirrhose und Carcinom der Leber und consecutiver carcinomatöser Infiltration des Peritoneums, Jahresb. u. d. Leistung. d. ges. Med. **1**: 226–227, 1867.
19. East, T.: Chiari's disease, with hypertrophic osteoarthropathy and familial lipomatosis, Proc. Roy. Soc. Med. **26**: 272, 1932.
20. Kretz, R.: Pathologie der Leber, Ergebn. d. allg. Path. u. path. Anat. **82**: 473–537, 1902.
21. Altschule, M. D., and White, G.: Chiari's syndrome in patient with polycythemia vera: report of case, New England J. Med. **220**: 1030–1033, 1939.
22. Berk, L.: Ueber Thrombose der Lebervenen nach umscriebener Thrombose im hepatischen Stück der unteren Hohlvene, Beitr. z. path. Anat. u. z. allg. Path. **90**: 509–512, 1932.
23. Cole, N. B.: Comments on case of polycythemia rubra vera with autopsy, M. Clin. North America **16**: 1255–1265, 1933.
24. Lüdeke, H.: Thrombophilie und Polycythemie, Virchows Arch. f. path. Anat. **293**: 218–252, 1934.

25. McAlpin, K. R., and Smith, K. E.: Polycythemia vera: report of fourteen cases treated with acetylphenylhydrazine, New York State J. Med. **38**: 101–109, 1938.
26. Norman, I. L., and Allen, E. V.: The vascular complications of polycythemia, Am. Heart J. **13**: 257–274, 1937.
27. Oppenheimer, B. S.: Vascular occlusion in polycythemia vera, Tr. A. Am. Physicians **44**: 338–344, 1929.
28. Churton, T.: Case of cirrhosis of liver, apparently due to congenital syphilis, with thrombosis of hepatic veins, Tr. Path. Soc. London **50**: 145, 1899.
29. Coronini, C., and Oberson, G.: Neue histologische Ergebnisse bei Endophlebitis obliterans hepatica, Virchows Arch. f. path. Anat. **298**: 251–297, 1936.
30. Jacobson, V. C., and Goodpasture, E. W.: Occlusion of entire inferior vena cava by hypernephroma, with thrombosis of hepatic vein and its branches, Arch. Int. Med. **22**: 86–95, 1918.

ADDITIONAL USEFUL REFERENCES

31. Baehr, G., and Klemperer, P.: Thrombosis of portal and of hepatic veins, M. Clin. North America **14**: 391–410, 1930.
32. Cabot Case no. 27431, New England J. Med. **225**: 661–663, 1941.
33. Cattan, R., Carasso, R., Frumusan, P., Lumbroso, P., and See, P.: Deux cas de syndrome de Budd-Chiari, Bull. et mém. Soc. méd. d. hôp. de Paris **69**: 435–439, 1953.
34. Detrie, P.: La thrombose des veines sus-hépatique (syndrome de Budd-Chiari), Presse méd. **60**: 392–393, 1952.
35. Fruhling, L., Roger, S., and Jobard, P.: Le syndrome hépatique de Chiari (occlusion des veines sus-hépatiques), Ann. méd. **52**: 696–733, 1951.
36. Hallock, P., Watson, C. J., and Berman, L.: Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, Arch. Int. Med. **66**: 50–61, 1940.
37. Koshy, P.: Chiari's syndrome, Indian M. Gaz. **86**: 556–558, 1951.
38. Simonds, J. P., and Callaway, J. W.: Anatomical changes in livers of dogs following mechanical constriction of hepatic veins, Am. J. Path. **8**: 159–166, 1932.

PREVENTION OF CEREBRAL EMBOLISM DURING MITRAL COMMISSUROTOMY: RESULTS IN 433 CONSECUTIVE CASES *

By Houck E. Bolton, M.D., *Philadelphia, Pennsylvania,* J. Ernest Delmonico, Jr., M.D., *Syracuse, New York,* and Charles P. Bailey, M.D., *Philadelphia, Pennsylvania*

One of the most dreaded complications attendant upon intracardiac surgery is the occurrence of embolization to the cerebral circulation, with its associated high mortality and morbidity. We are presenting a method for reducing the incidence of such episodes which seems to offer a practical approach toward the solution of this problem.

In a previous publication [1] we described the technic and presented a small number of cases in which it was used. The number of cases so handled is now 433, and it would seem that the figures are statistically significant. These cases are compared with 235 consecutive cases in which the same operation was performed prior to the adoption of specific protective measures against cerebral embolization, and the modified technic is described.

While the original report of 80 cases stated that there had been no instance of cerebral embolization, our subsequent experience necessitates correction of the implication that the technic described is infallible. From our previous experience we had learned that prevention is the only feasible method of dealing with this complication. No satisfactory way of treating cerebral embolism following cardiac operations, and especially after mitral valve surgery, has been found. So far as we have been able to determine, these are the first reports of results in cases in which a definite method of prevention was used.

Essentially, the method consists of occluding the left common carotid and the innominate arteries for brief periods during the manipulation of those regions of the heart most likely to contain thrombotic material or loosely attached calcific particles. Occlusion is accomplished by loops of umbilical tape placed around these vessels near their origin. It seemed logical that any thrombotic or other particulate matter, such as calcium, dislodged from the atrium or mitral valve during the operation would be prevented from reaching the brain by momentary occlusion of the arteries, and that the emboli would be carried to other parts of the body (the extremities, for example). The sequelae of peripheral embolization are not so tragic, and it is frequently possible for them to be removed by embolec-

* Received for publication March 3, 1954.
From the Dept. of Thoracic Surgery of the Hahnemann Medical College and Hospital, the Doctors Hospital, and the Bailey Thoracic Clinic, Philadelphia, with the support of the Mary Bailey Foundation for Heart and Great Vessel Research, Philadelphia.

tomy or treated by other measures. This theoretic assumption appears to us to be justified.

Technic

The left hemithorax is opened in preparation for mitral commissurotomy, the left lung is retracted downward, and the upper portion of the mediastinum is exposed. An incision in the mediastinal pleura is made between and parallel to the left phrenic and vagus nerves, just above the arch of the aorta. The left common carotid artery is located to the right of the left subclavian artery and is dissected from the surrounding tissue with as little

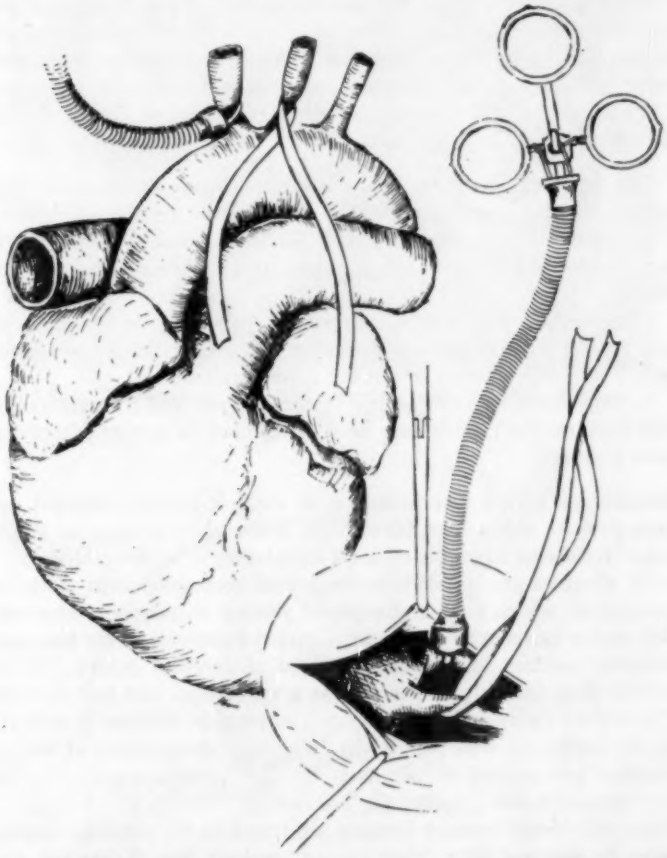


Fig. 1. Umbilical tape around the innominate artery and attached to a Rumel tourniquet for constriction as needed. Tape around left common carotid artery; occlusion accomplished by traction upon the tape to "kink" the vessels. Insert shows reflection of left mediastinal pleura and tapes applied to the arteries.

trauma as possible. After it has been mobilized, a strip of umbilical tape is passed beneath it (figure 1). Occlusion is subsequently accomplished by traction on the tape, which produces kinking of the vessel, for defined periods.

The innominate artery is then palpated with the left index finger and, using sharp and blunt dissection, it is mobilized with the aid of Rumel clamps. A strip of umbilical tape is then passed around the artery, and a Rumel tourniquet is applied.

It will be noted that this technic differs significantly from that originally proposed.[1]

When this has been done, the anesthetist palpates the temporal arteries to determine the effectiveness of the occlusion. When the surgeon is convinced that the vessels can be occluded at his election, he proceeds with the operation. The vessels are obstructed whenever dislodgment of thrombotic material or particles of calcium is considered likely. Specifically, this means at any time when:

1. The left atrial appendage is vigorously manipulated, as during the application of a purse-string suture at its base, during the placement of a clamp across the base of the appendage, and at the time an exploring finger is inserted into or removed from the left atrium through the appendageal incision.
2. The mitral valve is manipulated by palpating or applying digital pressure to the commissures, and during the use of the commissurotomy knives. This holds whether or not the valve is calcified.
3. A large intra-atrial thrombus is encountered and manipulated in the slightest fashion, the utmost care here being used in properly applying the occlusion technic.

The average period of obstruction of the left common carotid and innominate arteries is less than 60 seconds, followed by at least an equivalent interval of release to allow the cerebral circulation to be reëstablished. This allows an adequate amount of time for partial accomplishment of the operative procedure, which can be completed during subsequent intervals. In one case, under extreme adversity we occluded these vessels for two and one-half minutes without subsequent evidence of cerebral injury. However, we occlude them for only 90 seconds as a maximum, and feel that this interval is within the bounds of safety. The passage of time is indicated by one of the assistants, who begins rhythmic, audible counting at the rate of one number per second at the start of each manipulation. For double security the anesthetist "clocks" the interval.

When soft, newly formed thrombi are found in the auricular appendage, they may be removed by a "flushing-out" technic, but if they are well organized and attached to the atrial wall and bear "eel-like" streamers, they should be disturbed as little as possible (figure 2).

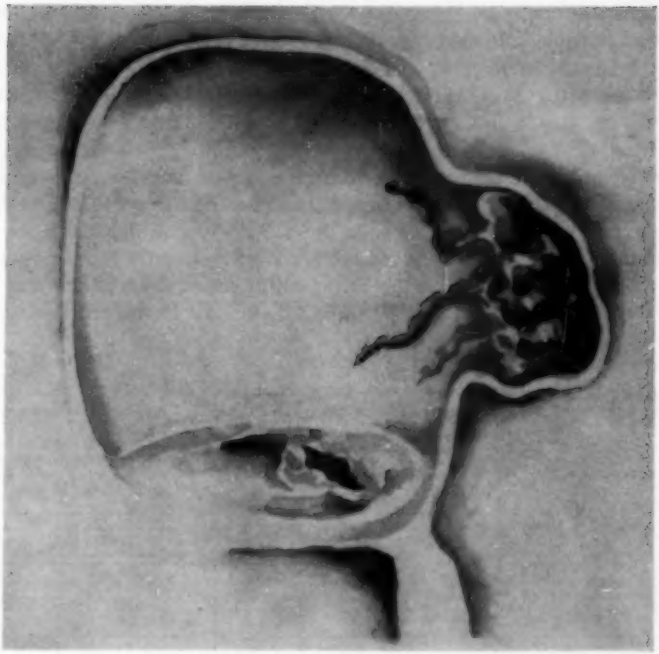


FIG. 2. Thrombus in left atrial appendage with "eel-like" streamers extending into the atrium.

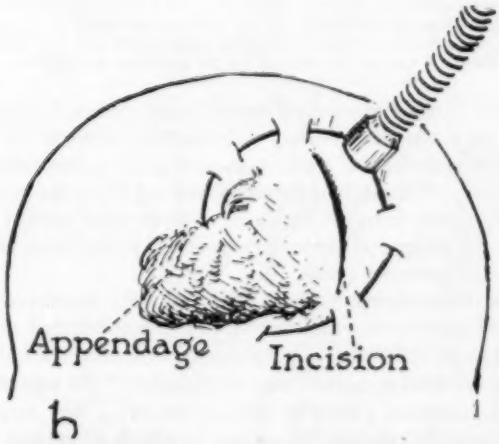


FIG. 3. Purse-string around base of thrombotic left atrial appendage and incision through atrial wall at site of entrance into atrium to avoid the thrombus.

Entrance of the finger through a thrombotic appendage should be avoided whenever possible. Instead, an approach through the left superior pulmonary vein, or, preferably, a direct entrance through the left atrial wall, should be chosen (figure 3).

Results

The advantage of protection over non-protection is shown by comparing the results in the 235 cases in which this method of preventing cerebral embolism was not used, with those in the 433 cases in which the innominate and common carotid arteries were occluded intermittently during operation (table 1). The reduction in the incidence of cerebral embolism was from 5.1 per cent in the unprotected group to 2.3 per cent in the protected group.

Table I

Comparison of Results in Patients with and without Protection against Embolization

	Mitral Commissurotomy without Protection against Cerebral Embolization 235 Consecutive Cases		Mitral Commissurotomy Using Technic for Protection against Cerebral Embolization 433 Consecutive Cases		
	No. of Cases	Per Cent	No. of Cases	Per Cent	
Cerebral Emboli	12	5.1	*10	2.3	One of these also had peripheral emb.
Peripheral Emboli (only)	None	0	5	1.15	
Mortality					
Cerebral	8	3.4	7	1.6	One of these also had peripheral emb.
Peripheral (only)	0	0	1	0.2	

* In two of these cases the assistant did not occlude the vessels at the critical moment. *If one deletes these two cases, the incidence of cerebral embolization with the technic described here is 1.8 per cent, as compared with an incidence of 5.1 per cent when not applied.*

In two of the 10 cases of cerebral embolization, the occlusion was handled improperly by an assistant. Perfect coördination between the surgeon and the assistant who occludes the arteries, at each point as indicated in the technic, is imperative. If these two cases are deleted from the series (and one might rightfully do so, for even though the tapes were applied the assistant failed to apply the technic at the critical moment), the incidence of cerebral embolization is 1.8 per cent (table 1).

The postoperative course in the 15 patients who developed emboli postoperatively (five peripheral and 10 cerebral) is summarized in table 2.

As we had expected, following the use of this procedure the percentage of those having cerebral embolism was decreased and the percentage of those with peripheral embolism (with or without cerebral) was increased.

In the previous 235 consecutive cases, in which protection against cerebral embolization was not applied, there were no (detectable) peripheral

emboli, the incidence of total embolization being 5.1 per cent, and the mortality rate in the series (3.4 per cent) was increased. In the following 433 consecutive cases in which our technic of cerebral protection against embolism was applied, the incidence of combined cerebral and peripheral embolization was 3.45 per cent, with a mortality rate (due to this complication) of 1.8 per cent.

One cannot expect the total number of emboli to become reduced. A very small embolus which would be large enough to produce cerebral injury

TABLE II

Summary of Postoperative Course in the 15 Patients with Embolization Despite Protection

Pt.	Age, Yrs.	Age, Mo.	Hosp.	Auricular Fibrillation	Hist. of Emb. Cere. or Periph.	Thrombus in Appendage	Calcification of Valve	Location of Cere. Embolus (Right or Left Side)	Location of Peripheral Emb. (Right or Left Side)	Treatment	Result	Notes	Carotid Thrombus
P. V.	31	1	Drs.*	+	+—P	+	0	Left	0		Death		
F. A.	47	1	H.H.†	+	0	+	0	0	Left femoral (artery)	Emb.	Death (cong. failure)		
A. L.	29	2	Drs.*	0	0	0	0	Left	0		Death		
V. G.	39	3	H.H.†	0	0	0	0	Left	0	Emb.	Recov.	Motor weakness on left improving.	
A. R.	46	4	H.H.†	+	0	0	0	Left	0	Emb.	Recov.	No embolus found	
M. Z.	39	5	H.H.†	+	+ C	+	+	Rt.	0		Death		
V. T.	38	2	H.H.†	+	+ C	+	+	0	Left femoral	Emb.	Recov.		
E. L.	39	3	H.H.†	+	0	+	0	0	Left femoral	Emb.	Left amput.		
B. D.	41	4	H.H.†	+	0	+	0	0	Left femoral	Emb.	Recov.		
L. G.	43	5	H.H.†	+	0	0	+	0	Left femoral	Emb.	Left amput.	Embolus not located	
C. B.	42	6	H.H.†	+	0	+	0	Rt.	Right femoral	Per. exp.	Death	No emb. in fem.	
L. H.	46	7	H.H.†	+	+ C	+	+	Rt.	0	Car. exp.	No emb.; death		
L. K.	48	8	Drs.*	+	+ P	0	0	Rt.	0		Death		
G. W.	47	9	Drs.*	+	+ C	0	+	Left	0		Death		
E. M.	39	10	Drs.*	+	+ C	+	0	Rt.		Car. emb.	Recov.		No hemiplegia. No residuum
Total cases				13	7	9	5						
Percentage (%)				86.6	46.6	60.0	33.3						

* Doctors Hospital.
† Hahnemann Hospital.
Emb. = Embolectomy.
Per. exp. = Peripheral exploration.
Car. exp. = Carotid exploration.
Car. emb. = Carotid embolectomy.

if lodged elsewhere may not produce symptoms and so may result in a so-called "silent embolus."

These silent emboli probably account for the discrepancy in the two figures for the total emboli, that is, one large enough to produce evidence of cerebral embolization may not be large enough to produce evidence of peripheral embolization.

Postoperative Sequelae and Discussion

Emboli: Carotid embolectomy or exploration was performed in four cases in which there was definite absence of pulsation of the artery. Three of the four patients survived. A thrombus was recovered in two instances and residual hemiplegia was present in two cases.

In all six of the patients who developed peripheral embolization the involved artery was explored, and the embolus was found and removed in four. The site of the arterial occlusion was the left femoral artery in five of the six cases. Amputation above the knee was necessary in two of the six cases. Routine oscillometric readings above and below the knee prior to mitral surgery have helped tremendously in evaluating the case postoperatively when peripheral embolization has been suspected. This is especially pertinent in the early postoperative period, when there may be hypotension which renders the pulsations of the peripheral vessels difficult to palpate.

Calcification of the mitral valve was present in three of the 10 cases with cerebral emboli, and death ensued in all three. As the authors,[1, 2] Harken [3] and others have pointed out, calcification of a valve predisposes to embolization.

The ages of the patients with embolism ranged from 29 to 48 years. It is generally accepted that the incidence of clotting is greater in the older age group, and yet Hall, Dencker and Biorck, in a study of 240 autopsy reports of patients with disease of the mitral valve (alone or with associated aortic involvement), found that embolism has occurred in a nine year old patient and was not infrequent in the second, third and fourth decades of life.[4]

Five of the cerebral emboli in our series were left-sided and five were right-sided. This is in agreement with the findings of Hall, Dencker and Biorck, who found the incidence to be essentially the same on both sides of the brain.[4]

Auricular Fibrillation and Thrombosis: Auricular fibrillation was present in eight of the 10 patients with cerebral emboli and in all of those with peripheral emboli. In neither of the two patients without fibrillation was a thrombus found in the appendage. In the entire group of 15 patients who had embolism, appendageal thrombi were demonstrated in all but six, which lends support to the observation that auricular fibrillation increases the risk

of dislodgment of an embolus at the time of operation,[5] as well as the tendency of embolism to occur.

In autopsies performed upon 89 patients who had undergone mitral valve surgery McGoon and Henly [6] found that (1) about half of those with auricular fibrillation had atrial thrombosis; (2) the great majority of those with atrial thrombosis had had fibrillation, and (3) of those with auricular fibrillation before operation, 13.5 per cent developed cerebral embolism during the period of anesthesia, whereas this occurred in only 2.8 per cent of the nonfibrillating group.

Although thrombi were not found in the appendages of six of the 15 patients who subsequently presented embolism (peripheral in one, cerebral in five), three of these six died of embolism, and in a fourth patient amputation of the left lower extremity was necessary because of embolism of the left femoral artery and gangrene. This would seem to place in disfavor resection or ligation of the auricular appendage for the purpose of eliminating the source of systemic arterial emboli in patients with mitral stenosis and recurring arterial emboli, as advocated by Madden [6] and others. Experimentally, Hellerstein, Sinaiko and Dolgin [7] demonstrated that this method was effective in dogs, but subsequent workers have found it to be inadequate in man. Arterial emboli recurred in three patients in whom Baronofsky [8] had ligated the left auricular appendage. Studies made by Graef et al.,[9] Soderstrom et al.[10] and Jordan et al.[11] suggest that this operation might be expected not to be effective. In individuals who had had rheumatic heart disease or mitral stenosis, or both, these investigators, working independently, found the appendage to be thrombosed in only about half of the cases. We have amputated the appendage in order to prevent embolism, but in our judgment it does not completely solve the problem, since the thrombi are not always confined to the appendage. Julian and others [12] likewise consider removal of the appendage of no value in this condition. In a series of 42 mitral commissurotomies performed by him and his group, thrombi were found in only one atrium, and yet two patients developed three episodes of embolism. Gagnon [13] calls attention to the unreliability of the palpating finger in evaluating the presence of thrombi in the atrium. In 25 of the 28 patients upon whom he had performed commissurotomy, the atrium was so large that his index finger would not reach the opposite wall. Wallach [14] reports that in 509 cases of rheumatic disease thrombi were found at autopsy in one or more chambers of the heart in 137 (26.9 per cent). Among the 295 with moderate to severe involvement of the mitral valve, 106 (35.8 per cent) had thrombi in the atrium or appendage, or both. Thrombi would thus seem to be closely associated with arterial embolism, but embolism occurs frequently in the absence of obvious visually or digitally recognizable atrial thrombosis.

Other Methods of Preventing Embolization: Obstruction of the carotid arteries by pressure upon them when the finger is inserted into the atrium has been reported to reduce the number of deaths from embolism.[15] The

pressure is exerted by the anesthetist at the signal of the operator. This would seem to be an acceptable method, provided the pressure is applied in such a manner that the carotid arteries are completely occluded but the carotid sinus reflex is not initiated, with subsequent production of bradycardia or cardiac standstill. Since the arteries most accessible for digital pressure are the internal carotid arteries (the site of the carotid sinuses), the method of occlusion of the innominate and common carotid arteries by encirclement near their origin would appear to be preferable because it obviates this risk.

Dicoumarin, given orally beginning with the second postoperative day, is used by Chalier [16] to prevent embolism after all types of surgery. He believes it to be not only useless but also unwise to give anticoagulants preoperatively. He has found oral therapy effective in most cases, without the need for determining the prothrombin time. Intravenous heparinization is reserved for individuals with a serious tendency to thrombophlebitis or phlebothrombosis. We have seldom used anticoagulant therapy in cardiac surgery because of the likelihood of hemorrhage.

Summary

1. A technic for the prevention of cerebral embolization during surgery of the mitral valve has been presented.

2. Results of the application of this technic revealed a reduction in the incidence of cerebral embolization from 5.1 per cent in the previous 235 consecutive unprotected group to 2.3 per cent in the following 433 consecutive cases. This incidence is reduced to 1.8 per cent if two cases in which the assistant failed to apply the technic properly are deleted from the group.

3. The mortality in the group in which cerebral protection was not applied was 3.4 per cent, as compared with 1.8 per cent mortality in the group in which protection against cerebral embolization was applied.

4. The relation of atrial fibrillation and atrial thrombosis to cerebral embolism is discussed.

BIBLIOGRAPHY

1. Bailey, C. P., Olsen, A. K., Keown, K. K., Nichols, H. T., and Jamison, W. L.: Commissurotomy for mitral stenosis. Technique for prevention of cerebral complications, J. A. M. A. **149**: 1085, 1952.
2. Bolton, H. E., Maniglia, R., and Massey, F. C.: Calcific emboli complicating mitral valve commissurotomy, J. Thoracic Surg. **24**: 502, 1952.
3. Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F.: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment, Circulation **3**: 349, 1952.
4. Hall, P., Dencker, S. J., and Biorck, G.: Studies in mitral stenosis. III. Observations on the incidence and distribution of cerebral emboli with regard to the possibilities of their prevention during operative procedures, Am. Heart J. **44**: 600, 1952.
5. McGoon, D. C., and Henly, W. S.: The significance of auricular fibrillation and auricular thrombosis in mitral valve surgery, Bull. Johns Hopkins Hosp. **91**: 419, 1952.

6. Madden, J. L.: Resection of the left auricular appendage. A prophylaxis for recurrent arterial emboli, J. A. M. A. **140**: 769, 1949.
7. Hellerstein, H. K., Sinaiko, E. S., and Dolgin, M.: Amputation of canine atrial appendage, Proc. Soc. Exper. Biol. and Med. **66**: 337, 1947.
8. Baronofsky, I. D.: Some recent aspects of cardiac and juxta-cardiac surgery, Minnesota Med. **33**: 339, 1950.
9. Graef, I., Berger, A. R., Bunim, J. J., and De la Chapelle, C. E.: Auricular thrombosis in rheumatic heart disease, Arch. Path. **24**: 344, 1937.
10. Soderstrom, H.: Myocardial infarction and mural thrombosis in the atria of the heart, Acta med. Scandinav. Suppl. 217, 1948.
11. Jordan, R. A., Scheifley, C. H., and Edwards, J. E.: Mural thrombosis and arterial embolism in mitral stenosis. A clinicopathologic study of 51 cases, Circulation **3**: 363, 1951.
12. Julian, O. C., Dye, W. S., Baker, L. A., and Sadove, M. S.: Surgical treatment of mitral stenosis, Arch. Surg. **65**: 621, 1952.
13. Gagnon, E. G., in discussion of Julian and others.[12]
14. Wallach, J. B., Lukash, L., and Angrist, A. A.: An interpretation of the incidence of mural thrombi in the left auricle and appendage with particular reference to mitral commissurotomy, Am. Heart J. **45**: 252, 1953.
15. Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F.: The surgery of mitral stenosis. III. Finger-fracture valvuloplasty, Ann. Surg. **134**: 722, 1951.
16. Chalier, A.: Quelques donnees sur les phlebites et embolies postoperatories et sur leur prophylaxis (Some practical facts concerning postoperative phlebitis and embolisms and their production), Lyon chir. **47**: 857, 1952.

EARLY RESULTS OF PROLONGED STREPTOMYCIN–PAS TREATMENT OF PULMONARY TUBERCULOSIS *

By ROGER S. MITCHELL, M.D., F.A.C.P., *Trudeau, N. Y.*

DESCRIPTION OF STUDY

THIS is a progress report [1] on all 331 patients at Trudeau Sanatorium who were given combined streptomycin-para-aminosalicylic acid (PAS) therapy for four months or more, between March, 1949, and January, 1954. Treatment was started in the last case in June, 1953; 68 patients were still receiving streptomycin-PAS in January, 1954. Most of the patients finished treatment in the charge of their private physicians after discharge. Contact has been maintained in 98 per cent of the cases.

Background features were as follows: The socio-economic status of the patients was well above average. The extent of disease was minimal in 22 per cent, moderately advanced in 62 per cent and far advanced in 16 per cent. Cavity was present at the outset in 48 per cent of the cases; the average diameter of the largest cavity in those with cavity was 1.7 cm. Sputum bacteriology was positive before treatment in 76 per cent.

Pretreatment drug status was as follows:	No.	%
Original treatment* (Orig):	237	72
Retreatment streptomycin and PAS sensitive (Re-Sens):	42	13
Retreatment streptomycin and PAS sensitivity unknown (Re-?):	28	8
Retreatment streptomycin and/or PAS resistant †(Re-Res):	24	7
Total	331	100%

* Two cases with primary streptomycin resistance were excluded from study.

† For the purpose of this analysis, streptomycin and PAS resistance have been arbitrarily defined as follows:

Streptomycin-resistance (a) Direct test (A.T.S. solid medium): significant growth in the tube containing approximately 3.5 mcg./ml. in comparison to control tube. (b) Subculture test (liquid medium): significant growth in 2.5 mcg. or more/ml. of liquid Tween-albumin medium observed for 14 days.

PAS-resistance: Direct and subculture tests (A.T.S. solid medium): significant growth in the tube containing approximately 1.0 mcg. or more PAS/ml. in comparison to control tube.

There were three Negroes, eight Orientals and 320 whites. The age range was 15 to 73, the median, 34. Fifty-five per cent were males. The use of nonsurgical collapse was: pneumoperitoneum, 27 per cent; pneumothorax, 3 per cent; and phreniclasis, 2 per cent. The use of surgery was as

* Received for publication February 26, 1954.

From Trudeau-Saranac Institute, Trudeau, N. Y. This study was made possible by a grant-in-aid from the Committee on Medical Research of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

Presented in part at the V. A., Army, Navy Conference on Chemotherapy of Tuberculosis, February 8–11, 1954, St. Louis, Missouri.

follows: resection, 25 per cent; thoracoplasty or plombage thoracoplasty, 9 per cent.

About 70 per cent received streptomycin, 1 gm. twice weekly throughout. In general, those on retreatment and those seriously ill received streptomycin, 1 gm. daily. Those past 50 received streptomycin, 0.5 gm. daily. All received 9 to 12 gm. of PAS (or 12 to 15 gm. sodium PAS) daily.

The duration of streptomycin-PAS treatment was as follows:

Months	Number of Cases
4–5	31
6–7	22
8–9	14
10–11	15
12–26	181
Still taking	68
Total	331

For purposes of statistical analysis, each case has been classified as a success or failure to date. A case was classified as a failure for *any* of the following reasons:

1. Presence of cavity *eight* or more months after start of treatment.
2. Sputum (or gastric washing) culture positive for *Mycobacterium tuberculosis eight* or more months after start of treatment.
3. Roentgenographic spread of pulmonary tuberculosis or *new* appearance of cavity at *any* time after start of treatment.
4. Development or relapse of extrapulmonary tuberculosis after start of treatment.

Results

Incidence and Speed of Cavity Disappearance and Culture Conversion: In figure 1 will be found the incidence and speed of cavity disappearance in the 159 cases with cavity before treatment, subdivided by the pretreatment drug status. These computations were made by the Life Table method; when cavity was still open at resection the case was included as open to that time. It is evident that original treatment is more effective on cavity (75 per cent disappearance at eight months) than retreatment in drug-sensitive cases (40 per cent disappearance at eight months). The difference was most striking, however, in those with drug resistant organisms present before retreatment (25 per cent disappearance at eight months).

There was also a tendency for cavities which are going to disappear to do so within six to eight months.

The incidence and speed of culture conversion have been determined and recorded in similar manner for the 232 cases with positive cultures before treatment (figure 2). The findings were essentially the same as for cavity disappearance except that there was a higher (over 90 per cent of original

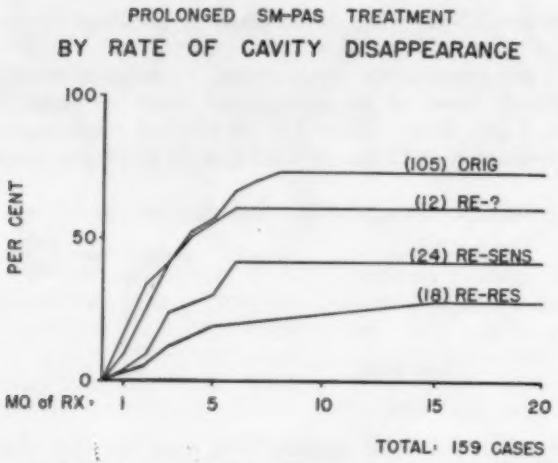


FIG. 1. Incidence and speed of disappearance of cavity during prolonged streptomycin-PAS treatment by pretreatment drug status.

treatment cases at six months) over-all proportion and earlier occurrence (usually by five or six months) of culture conversion than of cavity disappearance. Those with drug-resistant organisms in sputum before retreatment presented a poor outlook for conversion.

Classification of Failures: Failure, as defined, had occurred in 59 (18 per cent) of the 331 cases by January, 1954. The distribution of six fac-

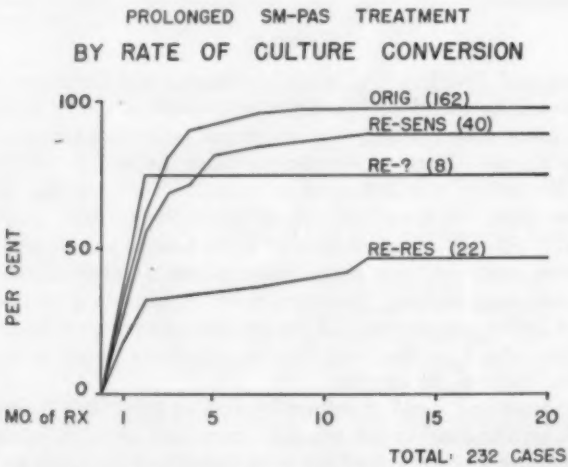


FIG. 2. Incidence and speed of sputum (and/or gastric washing) culture conversion during prolonged streptomycin-PAS treatment by pretreatment drug status.

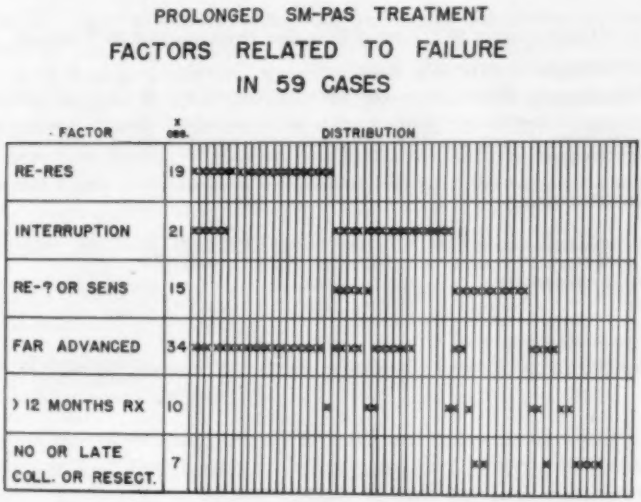


FIG. 3. Relationship of various factors to failure of prolonged streptomycin-PAS treatment.

tors considered related to the failure of streptomycin-PAS treatment is shown in figure 3. There is no longer any doubt about the close correlation between in vitro and in vivo streptomycin resistance. Evidence relating in vitro with in vivo PAS resistance is presented below in figure 4. It has been

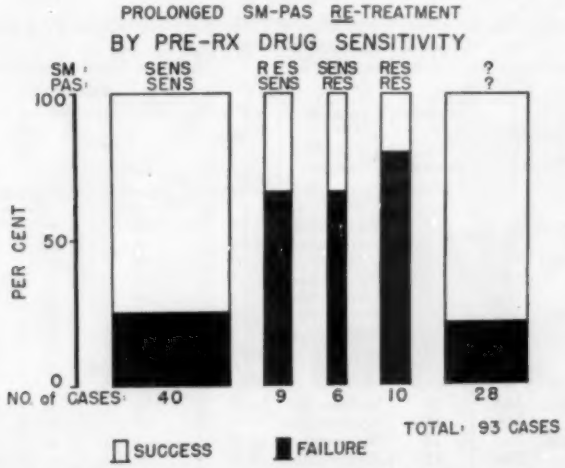


FIG. 4. The influence of pretreatment streptomycin and PAS sensitivity on the early results of prolonged streptomycin-PAS retreatment. The size of the blocks and any subdivisions thereof are proportionate to the size of the sample.

TABLE I

Brief Descriptions of 59 Failures of Prolonged Streptomycin-PAS Treatment

I.	Failure *during* streptomycin-PAS therapy		
	A. Delay in cavity disappearance and/or culture conversion to 9, 9, 11 and 16 months		4
	B. Unfavorable roentgenographic change: (1) cavity opened in 15th month and promptly disappeared; (2) spread in 5th month which cleared after isoniazid was immediately added to regimen		2
	C. Disease controlled only after the introduction of other treatment after 8 months or more of streptomycin-PAS		
	Resection	12	
	Resection + isoniazid	3	
	Isoniazid	8	
	Thoracoplasty	2	
			25
	D. Disease never controlled		15
II.	Relapse *after* successful completion of streptomycin-PAS treatment (see table 2)		13
	Total		59

observed that retreatment is less effective than original treatment even when organisms were streptomycin-sensitive before retreatment.[2] The apparently adverse effects of interruptions of therapy and of far advanced disease are shown in figures 6, 7 and 8. Evidence of the importance of continuing streptomycin-PAS treatment for no less than 12 months in any case is rapidly accumulating. Failure to collapse or resect persistent cavities was considered at least partly responsible for failure in seven cases. In four, none of these factors was present.

The 59 failures are described briefly in table 1.

TABLE II

13 Relapses after Successful Completion of Prolonged Streptomycin-PAS Treatment in 217 Cases

Patient	Pre-Treatment Drug Status	N.T.A. Class	Duration of Streptomycin-PAS (months)	Month of Resection During Streptomycin-PAS Treatment	Relapse				
					Months after End of Streptomycin-PAS Treatment	X-Ray		Sputum Bacteriology	
						Spread	Cavity	Smear	Culture
TB	Re-Sens.	Mod.	4	No resection	9	+	+	+	+
MA	Re-?	Min.	4	No resection	24	+	+	+	+
GK	Re-Sens.	Mod.	16	12th	10	+	+	+	+
EF	Orig.	Far	4	No resection	3	?	?	?	+
DB	Orig.	Mod.	4	No resection	5	0	0	0	+
JL	Re-Res.	Mod.	4	No resection	17	0	0	0	+
AB	Orig.	Mod.	12	No resection	8	+	0	0	+
TO	Orig.	Mod.	4	2nd	22	0	0	+	0
PH	Orig.	Min.	10	2nd	6	Pleurisy with effusion	0	0	0*
EW	Re-Sens.	Mod.	18	No resection	5	0	0	+	0
BG	Orig.	Min.	17	No resection	9	0	+	0	0
MP	Re-Res.	Far	19	No resection	6	+	0	0	0
EI	Orig.	Far	18	No resection	9	0	+	0	0

* Both pleural fluid and gastric washing cultures negative.

The 13 "relapses" after apparently successful completion of treatment are described in more detail in table 2. These 13 patients had achieved cavity disappearance, culture conversion and a relatively stable roentgenographic appearance before stopping streptomycin-PAS treatment. Additional information on the timing of these relapses and their relation to the use of resection, extent of disease and presence of cavity is given in tables 4, 5, 6 and 7.

TABLE III

January 1954 Status (by Early Clinical Results) of 331 Patients Who Received Streptomycin-PAS for Four Months or More

Condition	"Success"	"Failure"	Total
Well	269	37	306
Sick—Tuberculosis	0	14	14
Dead—Tuberculosis	0	5	5
Dead—Nontuberculous Cause	1	2	3
Contact Lost	2	1	3
Total			331

The January, 1954, status of the 331 patients is shown in table 3.

Retreatment: The effect of the pretreatment in vitro drug sensitivity on results with retreatment is shown in figure 4. The effect of prior use of one or both drugs, regardless of the sensitivity findings, is similarly illustrated in figure 5. It appears that PAS resistance (figure 4), and even a history of taking PAS alone (figure 5), are related to "failure" as much as streptomycin resistance and a history of taking streptomycin alone. In

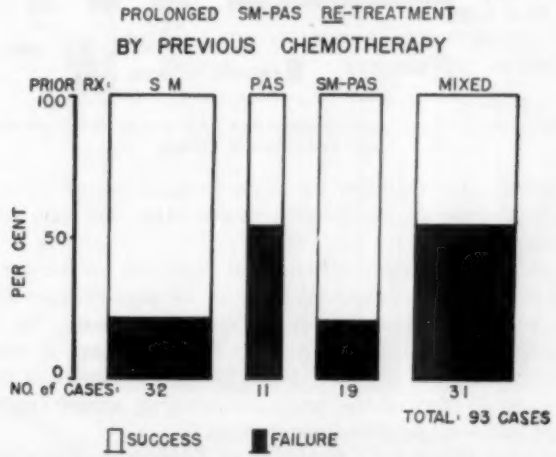


FIG. 5. The influence of prior courses of streptomycin, PAS, and streptomycin-PAS on the early results of prolonged streptomycin-PAS retreatment.

vitro drug resistance was found before retreatment less frequently when both drugs had previously been taken simultaneously rather than separately. Clinical results in these cases were correspondingly favorable (figure 5).

Extent of Disease: The influence of extent of disease and the pretreatment drug status is shown in figure 6. There was no great difference in the results in minimal and moderately advanced; on the other hand, about 40 per cent of patients with far advanced disease on original treatment have been failures. While those on original treatment fared better than those receiving retreatment with organisms found sensitive to both drugs, the differences were not great. This finding may have been influenced by the higher proportion of advanced disease in the retreatment than in the original

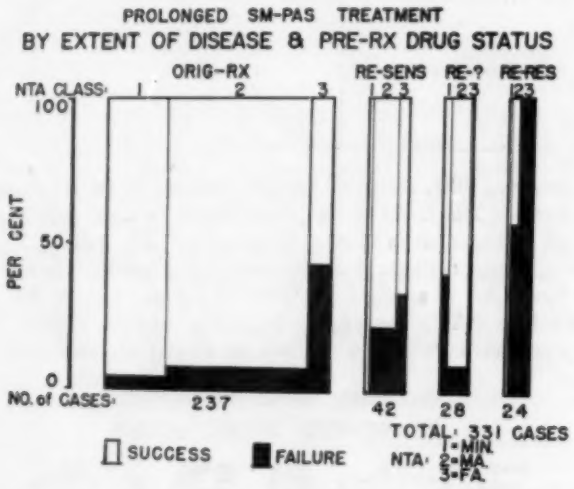


FIG. 6. Early results of prolonged streptomycin-PAS treatment by pretreatment drug status and extent of disease.

treatment group. On the other hand, the frequent use of daily rather than twice weekly streptomycin in the retreatment cases may have been a factor in their favor.

Interruption: Interruption of treatment is defined for the purpose of this analysis as no streptomycin and/or PAS for 14 days or more at some time during the period of chemotherapy, or frequent difficulty in maintaining regular PAS dosage. Interruption was found to have a seemingly unfavorable relationship to results. This was true, exclusive of the extent of disease (figure 7) and of the pretreatment drug status (figure 8), and decisively so in the original treatment group.

Relapse after Successful Completion of Treatment: There were 202 patients who completed original streptomycin-PAS treatment or drug sensi-

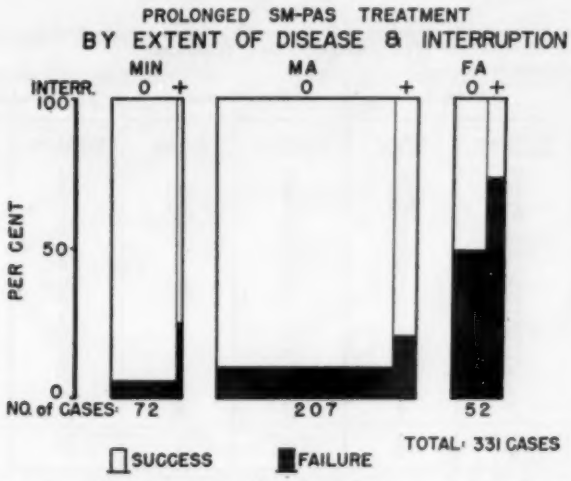


FIG. 7. Early results of prolonged streptomycin-PAS treatment by extent of disease and and interruption of therapy.

tive retreatment with apparent control of disease, i.e., no evidence of cavity by planigram, repeated negative cultures, and relatively stable serial chest roentgenograms. Fifty-eight of these had pulmonary resection during therapy. They have been followed for from three to 42 (average, nine) months after completion of therapy.

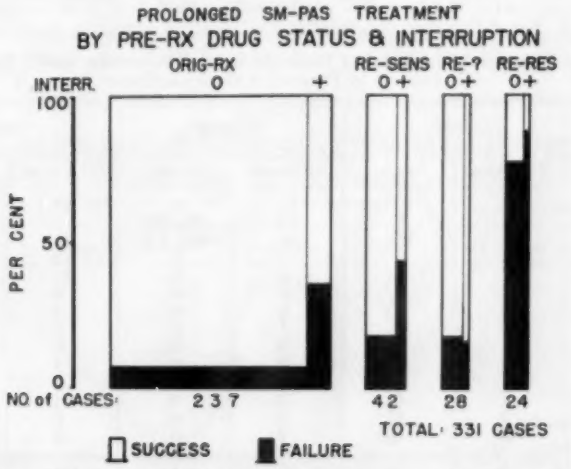


FIG. 8. Early results of prolonged streptomycin-PAS treatment by interruption of therapy and pretreatment drug status.

TABLE IV

Relapse after Successful Completion of Prolonged Original Streptomycin-PAS Treatment: 171 Patients by Extent of Disease

Months after End Streptomycin-PAS	Minimal		Mod. Advanced		Far Advanced	
	No Relapse	Relapse	No Relapse	Relapse	No Relapse	Relapse
3	20	0	35	0	5	EF
6	10	PH	9	DB	2	0
9	12	BG	14	AB	0	EL
12	2	0	8	0	0	0
15	2	0	8	0	1	0
18	2	0	6	0	0	0
21	0	0	5	TO	0	0
24	3	0	4	0	0	0
27	1	0	4	0	1	0
30	1	0	4	0	0	0
33	1	0	1	0	1	0
36	0	0	1	0	0	0
39	0	0	0	0	0	0
42	0	0	1	0	0	0
Totals	54	2	100	3	10	2

There have been 10 relapses in these 202 patients to date, seven in the 171 who received original treatment and three in the 31 who received retreatment. The timing of each relapse or the months of follow-up without relapse for each case is shown in tables 4, 5 and 6 (original treatment) and table 7 (retreatment).

The original treatment cases are subdivided by extent of disease (table 4), presence of cavity (table 5) and use of resection (table 6). The initials in these tables refer to the individual cases which have relapsed; these

TABLE V

Relapse after Successful Completion of Prolonged Original Streptomycin-PAS Treatment: 171 Patients by Presence of Cavity at Outset

Months after End Streptomycin-PAS	Cavity		No Cavity		Total	
	No Relapse	Relapse	No Relapse	Relapse	No Relapse	Relapse
3	18	EF	42	0	60	1
6	6	0	15	PH, DB	21	2
9	10	EL	16	BG, AB	26	3
12	5	0	5	0	10	0
15	7	0	4	0	11	0
18	2	0	6	0	8	0
21	5	TO	0	0	5	1
24	2	0	5	0	7	0
27	1	0	5	0	6	0
30	2	0	3	0	5	0
33	1	0	2	0	3	0
36	1	0	0	0	1	0
39	0	0	0	0	0	0
42	0	0	1	0	1	0
Totals	60	3	104	4	164	7

TABLE VI

Relapse after Successful Completion of Prolonged Original Streptomycin-PAS Treatment: 171 Patients by Use of Resection

Months after End Streptomycin-PAS	Resection		No Resection		Total	
	No Relapse	Relapse	No Relapse	Relapse	No Relapse	Relapse
3	14	0	46	EF	60	1
6	3	PH	18	DB	21	2
9	7	0	19	EL, BG, AB	26	3
12	3	0	7	0	10	0
15	4	0	7	0	11	0
18	3	0	5	0	8	0
21	2	TO	3	0	5	1
24	2	0	5	0	7	0
27	1	0	5	0	6	0
30	2	0	3	0	5	0
33	0	0	3	0	3	0
36	0	0	1	0	1	0
39	0	0	0	0	0	0
42	0	0	1	0	1	0
Totals	41	2	123	5	164	7

relapsed cases, similarly identified, are described in more detail in table 2. Patients EF, DB and AB are the only relapses to date with positive cultures after original treatment. The other relapses have had new shadows, cavity, acid-fast bacilli on smear, or pleurisy with effusion, without confirmation by the finding of *Myco. tuberculosis* on culture. These might be labeled "partial" relapses for the present.

It is unfortunate that one third of the group has been followed for only three months or less, and only 61 have been followed for 12 months or more.

It is worth noting that the relapses of patients EF and DB both occurred within six months after finishing only four months of streptomycin-PAS.

TABLE VII

Relapse after Successful Completion of Prolonged Streptomycin-PAS Retreatment in Patients with Drug-Sensitive Organisms before Retreatment: 31 Cases by Use of Resection

Months after End Streptomycin-PAS	Resection		No Resection		Total	
	No Relapse	Relapse	No Relapse	Relapse	Nc Relapse	Relapse
3	3	0	4	0	7	0
6	2	0	3	EW	5	1
9	2	GK	0	TB	2	2
12	2	0	2	0	4	0
15	1	0	1	0	2	0
18	1	0	0	0	1	0
21	1	0	2	0	3	0
24	0	0	1	0	1	0
27	2	0	0	0	2	0
30	0	0	1	0	1	0
Totals	14	1	14	2	28	3

It will be seen in table 2 that patient AB had an overt clinical relapse in spite of 12 months of original treatment.*

Comment

The significance of the "partial" relapses, i.e., the last six described in table 2, is not entirely clear. Are the instances of new roentgenographic shadows, pleurisy with effusion, or the appearance of cavity without accompanying positive bacteriology the precursors of true tuberculous relapse? What is the significance of the finding of acid-fast bacilli with no growth of *Myco. tuberculosis* on culture of the same material?

By the same token, what is the significance of the two "failures" *during* chemotherapy (table 1, under I-B)? The significance of the spread immediately treated with isoniazid must remain obscure. The patient with the appearance (followed by prompt disappearance) of cavity in the fifteenth month of a 24 month course of streptomycin-PAS had resection of the involved segment in the eighteenth month. The pathologist reported "an essentially healed, non-necrotic lesion." The tissue bacteriology was entirely negative on smear, culture and guinea pig inoculation. Is such an event biologically favorable to the healing of tuberculosis? Several more years of follow-up will be required to provide the answers.

The answers to these questions may be secured sooner if observers consider that streptomycin-PAS may possibly be *definitive* treatment for tuberculosis at least in selected cases. Pessimists, remembering the sad experience with many other remedies in the past 50 years, are prone to conclude, often on slight provocation, that new therapies for tuberculosis are failures. Such thinking may cause delay in recognizing a cure when it comes along.

There appears no doubt about the adverse effect of interruptions of treatment (figures 7 and 8), and about the importance of treatment lasting more than four months (table 2). The data on the importance of prior PAS treatment (figure 5) and PAS resistance (figure 4) are admittedly limited but are hard to come by. As far as they go, they emphasize a point not generally recognized.

The present report has purposely omitted a consideration of the place of pneumoperitoneum in prolonged streptomycin-PAS therapy, since this has been reported elsewhere.[3] Trudeau Sanatorium policy during the study period has been to use pneumoperitoneum mostly for cavitary disease, and then mostly in patients with cavities of 1 cm. in diameter or larger.

The observations that cultures which are going to convert usually do so within five or six months (figure 2), and that cavities disappear within six

*Another overt clinical relapse was discovered after this report was prepared. It occurred 7 mos. after completion of 12 mos. of original streptomycin-PAS for a moderately advanced lesion in a diabetic female aged 30 whose residual lesion was resected during the seventh month of chemotherapy.

to eight months (figure 1), have been helpful in deciding when resection is indicated during prolonged streptomycin-PAS treatment.

Summary

1. Early results of prolonged streptomycin-PAS-rest treatment of pulmonary tuberculosis have been very favorable in 331 consecutive patients so treated at Trudeau Sanatorium in the years 1949 to 1954.

2. Success with original streptomycin-PAS treatment is apparently at least partly dependent upon the avoidance of interruptions in therapy, the extent of the lesion and prolonged administration.

3. If a cavity is going to disappear during prolonged streptomycin-PAS treatment, it is apt to do so within six to eight months; if cultures are going to convert, they are apt to do so within five to six months.

4. Prior *PAS* therapy and in vitro *PAS* resistance have just as adverse an influence on results with prolonged streptomycin-PAS retreatment as prior *streptomycin* therapy and in vitro *streptomycin* resistance.

5. The significance of "partial" relapses after apparently successful completion of prolonged streptomycin-PAS treatment has yet to be determined.

BIBLIOGRAPHY

1. Mitchell, R. S., Meade, G. M., and Steenken, W., Jr.: Analysis of failures of prolonged streptomycin-PAS treatment of pulmonary tuberculosis, Transactions 12th Conference Chemotherapy Tuberculosis, VA, Army, Navy, Atlanta, Ga., Feb., 1953, p. 92.
2. Tucker, W. B.: Comparison of therapeutic effects of randomized chemotherapeutic regimens employed in the treatment of pulmonary tuberculosis, Transactions 10th Conference Chemotherapy Tuberculosis, VA, Army, Navy, Atlanta, Ga., Jan., 1951, p. 42.
3. Brinkman, G. L., and Mitchell, R. S.: The use of pneumoperitoneum during prolonged streptomycin-PAS treatment of pulmonary tuberculosis, Am. Rev. Tuberc. **69**: 963, 1954.

MORTALITY RATES IN ACUTE MYOCARDIAL INFARCTION. III. THE RELATION OF PATIENT'S AGE TO PROGNOSIS *

By SIDNEY SCHNUR, M.D., F.A.C.P., *Houston, Texas*

THE influence of the patient's age upon the mortality rate and the significance of age as a prognostic factor in acute myocardial infarction have long been subjects of dispute. All varieties of opinion have been expressed, including those of Rosenbaum and Levine,[1, 2] who contend that increased age is reflected in an increased mortality rate; Stroud,[3] who states that "closure of a coronary artery in a relatively young person is said to carry with it a more serious prognosis than in an older person"; and Russek,[4] who asserts that age of itself is not an important prognostic factor in acute myocardial infarction. The solution of this problem would appear to be simple, but obviously such has not been the case. The method of study usually employed, of comparing the mortality rate of patients in one age group with that of patients in another, is statistically unacceptable because there is no certainty that other factors important in prognosis are present in equal degree in both groups. The finding of a difference in the mortality rate in such investigations could be due to other prognostic inequalities or dissimilarities in the groups rather than to age per se. A more satisfactory method of study to determine whether the patient's age may be useful in predicting recovery is to select patients who are equally ill on admission to the hospital, and then to determine whether there is any significant difference in the mortality rate in the various age groups. A recently proposed method for measuring quantitatively severity of illness in this disease has provided the technic necessary to investigate the problem in such manner.[5]

METHODS AND MATERIAL

The clinical records of patients admitted with acute myocardial infarction to Jefferson Davis Hospital from 1941 to 1952 and to the Methodist, Veterans Administration and Southern Pacific Hospitals in 1951 and 1952 were reviewed. Only those records in which the diagnosis could be reasonably substantiated by the usually accepted criteria were selected for this study. Patients dying within 24 hours of admission were not included. The Pathologic Index Rating, a scoring system which assesses quantitatively degrees of illness in this disease, was determined for each of the 399 admissions, and, depending upon the rating, patients were placed into one of five

* Received for publication January 18, 1954.
From the Department of Medicine, Baylor University College of Medicine, and the Jefferson Davis, Methodist, Veterans Administration and Southern Pacific Hospitals, Houston, Texas.

groups which reflected increasing degrees of severity of illness upon admission, i.e., 0 to 19 (mild), 20 to 39 (moderate), 40 to 59 (moderately severe), 60 to 79 (severe), 80 and above (critical). The number of patients and mortality rate for each group were ascertained. Each pathologic index rating group was then subdivided according to the patient's age into the following age classification, i.e., 30 to 45, 46 to 60, 61 to 75, 76 and above, and similar studies were undertaken of each age group. Finally, each age classification was studied for its percentage distribution among the various pathologic index rating groups.

Results

The data are presented in table 1. Because of a comparatively few patients in several categories, no unequivocal statement can be made concerning the statistical significance of these findings.* However, a definite trend is discernible. When patients are classified according to their patho-

TABLE I

Mortality Rate Correlated with Age and Pathologic Index Rating

Age	0–19			20–39			40–59			60–79			80+			Total		
	Cases	Deaths	Mort. Rate (Per Cent)	Cases	Deaths	Mort. Rate (Per Cent)	Cases	Deaths	Mort. Rate (Per Cent)	Cases	Deaths	Mort. Rate (Per Cent)	Cases	Deaths	Mort. Rate (Per Cent)	Cases	Deaths	Mort. Rate (Per Cent)
30–45	25	2	8	20	3	11	9	2	22	4	1	25	3	3	100	61	11	18
46–60	63	2	3	43	5	12	26	4	15	16	9	56	10	8	80	158	28	18
61–75	41	3	7	40	7	18	27	9	33	23	14	61	21	19	90	152	52	34
76+	—	—	—	4	2	50	10	6	60	8	8	100	6	6	100	28	22	79
Total	129	7	5	107	17	16	72	21	29	51	32	63	40	36	90	399	113	28

Distribution of Patients in Different Age Groups According to Pathologic Index Rating

Age Group	0–39 P.I.R. (Per Cent)	0–59 P.I.R. (Per Cent)	60 + P.I.R. (Per Cent)
30–45	74	89	11
46–60	67	84	16
61–75	53	71	29
76+	14	50	50

logic index rating, the mortality rate is lowest and comparable in the 30 to 45 and 46 to 60 age groups, slightly higher in patients 61 to 75 years of age, and definitely greater in those above 75 years of age. Whether the increased death rate in those above 60 years of age is specifically due to this

* It is to be noted that if one additional death had occurred among the youngest patients of the severely ill (P.I.R., 60 to 79) group, there would have been no significant difference between the mortality rates of the various age groups in this classification.

disease, or may be considered a manifestation of the nonspecific decreased life expectancy associated with advancing age, is uncertain, but apparently a somewhat analogous observation was made in a group of consecutively selected patients admitted to the medical service without classification into diagnostic categories.† Age had no influence on the mortality rate of the mildly ill (P.I.R., 0–19), since the rate was less than 10 per cent at all ages, nor did it influence survival of the critically ill (P.I.R., 80 plus), for approximately 90 per cent of patients of all ages died.

A study of the distribution of cases among the pathologic index rating groups revealed a fairly parallel situation in the 30 to 45 and 46 to 60 age groups, with a large preponderance of cases in the mildly or moderately ill groups and a small percentage in the severely or critically ill groups. As the age increases, the tendency is for patients to enter the hospital in a more seriously ill condition, as indicated by a progressively smaller proportion of cases in the mildly ill group and a relatively increasing number of severely ill and critical patients. The crude mortality rate computed for the total number of all patients in each age group is a reflection of this "skewed" distribution.

These findings may be summarized as follows: (a) The mortality rate is higher in the older age group than in the younger age group because a larger proportion are seriously ill on admission and possibly because of the nonspecific factor of decreasing life expectancy. (b) The average age of seriously ill patients admitted to the hospital with acute myocardial infarction is higher than that of those less seriously ill. (c) In patients who are equally ill on admission, no striking difference in the mortality rate is found between any of the age groups except in those above 75 years of age. (d) Patients over 75 years of age are much more likely to be seriously ill on admission and to have higher mortality rate than younger persons who enter in a similar clinical state. (e) Young persons seriously ill on admission have a higher mortality rate than less seriously ill older patients. (f) The condition of the patient on admission to the hospital (pathologic index rating) is a vastly more important determinant of prognosis than the patient's age.

Conclusions

The clinical condition of the patient immediately following acute myocardial infarction may be considered to be the resultant of two opposing forces, i.e., the sudden initial assault of the infarction versus the body de-

† This study was undertaken to determine the mortality rate of patients classified into similar age groups who were admitted to the medical service of Jefferson Davis Hospital and selected consecutively without regard to diagnosis. The age group, total number of cases and mortality rate in a series of 547 patients were as follows: 30 to 45, 112 cases, 12 per cent; 46 to 60, 148 cases, 17 per cent; 61 to 75, 209 cases, 29 per cent; 76 plus, 88 cases, 39 per cent. Acute myocardial infarction accounted for 7 per cent of these admissions. This evidence of increasing mortality rate with advancing age is somewhat similar to the findings in acute myocardial infarction. The most striking difference between these studies, however, is the much higher mortality rate in patients above 75 years of age who were diagnosed myocardial infarction as compared to the unclassified group.

fense. Age is one of the many factors which affect the total defensive force. Other things being equal, increased age—by allowing additional time for the accumulation of the ills and infirmities of body and spirit—tends to weaken the defense against the myocardial insult, resulting in a more precarious clinical state. This study indicates that older persons are much more likely to enter the hospital in a more vulnerable condition than younger patients. From the clinical viewpoint, within the first 24 to 48 hours, and usually by the time the patient has been admitted to the hospital, the age factor has already had its maximal impact upon prognosis. The pathologic index rating is an attempt to express quantitatively by a single score the clinical status of the patient caused by the interplay of these forces determined on admission to the hospital. Thereafter, the patient's prognosis is gauged by his clinical appearance and by the presence or absence of specific factors known to influence recovery. During the period of hospitalization, the patient's age per se appears to have no more value in predicting recovery from this disease than it has in any other medical disease severe enough to require hospitalization. For example, a 62 year old person who suffers an acute myocardial infarction is likely to be more seriously ill on admission to the hospital, as determined by the pathologic index rating, and therefore to have a poorer prognosis than a 45 year old patient. However, if the clinical condition of both patients on admission happens to be similar, their relative chances of recovery depend upon the difference in life expectancy at their respective ages, a factor which is so much less important than the occurrence of shock, heart failure, arrhythmias, thrombo-embolism, etc. This probably does not apply to those above 75 years of age, who not only are prone to be more seriously ill on admission, but also to have a decidedly worse outlook than younger individuals entering in a comparable clinical state.

Summary

1. The present dispute concerning the relation of the patient's age to prognosis in acute myocardial infarction was discussed.

2. This problem was investigated by using a technic recently proposed which permits quantitative determination of severity of illness on admission to the hospital.

3. The principal findings were: (a) Patients who are admitted to the hospital in a seriously ill condition are generally older than those who are mildly ill on admission, and this factor is primarily responsible for the observation that higher mortality rates are found in groups with higher average age. (b) In patients who are equally ill on admission, a comparison of the mortality rate at various age levels reveals a slightly higher death rate in the older patients, which may possibly be due to the nonspecific progressively increasing death rate associated with advancing age. (c) The patient's age per se is of no value in predicting recovery from this disease for those who enter the hospital mildly or critically ill, is probably of limited

value for seriously ill patients, and is of definite value for all those above 75 years of age. (d) In general, the patient's age is a decidedly less important prognostic factor than the determination of his condition on admission (pathologic index rating), or the appearance during the course of the disease of specific clinical states known to affect prognosis adversely.

ACKNOWLEDGMENTS

The author is indebted to Dr. Willard A. Glass, Dr. Ray Goens, Dr. Henry D. Rosenblatt, Dr. George Spikes and Mrs. F. Brown, R.N., for assistance in obtaining a portion of the material included in this report.

BIBLIOGRAPHY

1. Rosenbaum, F. S., and Levine, S. A.: Clinical and electrocardiographic features of acute myocardial infarction on immediate prognosis, Arch. Int. Med. **68**: 913, 1941.
2. Rosenbaum, F. A., and Levine, S. A.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction, Arch. Int. Med. **68**: 1215, 1941.
3. Stroud, W. B.: The diagnosis and treatment of cardiovascular disease, 1946, F. A. Davis, Philadelphia, p. 713.
4. Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S., and White, L. G.: Age and survival in cases of acute myocardial infarction, J. A. M. A. **147**: 1731, 1951.
5. Schnur, S.: Mortality rates in acute myocardial infarction. II. A proposed method for measuring quantitatively severity of illness on admission to the hospital, Ann. Int. Med. **39**: 1018, 1953.

VARYING CLINICAL MANIFESTATIONS OF DEPRESSION *

By Sylvan H. Robertson, M.D., *Chicago, Illinois*

The non-psychiatrist, the internist primarily, encounters patients in whom depression is not easily recognized. Variations in the symptoms do not point to the primary syndrome. Both the patient and the doctor may be unaware that the patient is depressed. The doctor's preoccupation with the physical complaints that may be suggestive of pathologic organic alterations produces a search for somatic disease and, when no disease is found, the patient is left with the hollow reassurance that he is well. The diagnosis becomes psychoneurosis and, if the patient can continue to work, the physician may feel that his job is done.

It is my impression, shared by many physicians, that the symptom of depression in individuals in our society has been increasing, not only because depression is more widely recognized, but also because of an actual increase in incidence. Basically this has been explained by various authors as a result of hostility and aggression which have no adequate outlet. The conflictual situations which may produce the symptoms of depression are numerous and are frequently the source of deep personality disturbances. That depression lessens the mental acuity and decreases the individual's functional and integrative capacity is well understood.

Psychiatrists encounter depression as a major syndrome. The presenting complaint may be a mood fixation, or depression may occur in the course of therapy as the patient encounters conflicts which are unbearable. The non-psychiatrist, on the other hand, may recognize depression as a symptom or syndrome, but frequently the mood fixation is covered up, masked, intermingled with physical symptoms, and is not clearly differentiated. It is this group of patients with whom I have concerned myself in this paper.

Dynamic psychiatry recognizes that depression may be a defense against an impending breakdown of the personality. The corollary, that physical symptoms may be a defense against a deep depression, has also been discussed.

Depression is recognized as a syndrome in which there is a mood fixation so that the patient may feel melancholy, blue, sad, lonesome, worried, afraid or homesick. It may be expressed in the manner of speech, in facial expression or as depressive mood equivalents. The patient may express content appropriate to the mood, such as self-derogatory or self-depreciatory ideas, guilt or sin. Suicidal preoccupation may be prominent. There may be a

* Received for publication January 29, 1954.
From the Department of Internal Medicine, University of Illinois, and the Department of Medicine, Michael Reese Hospital, Chicago.

general slowing of motility, of speech, and of the thinking process. Important physiologic alterations, such as insomnia or early awakening, poor appetite, weight loss, fatigue, constipation, reductions in sexual functions, with amenorrhea in the female, are the common symptoms that may or may not be present. When a few of the aforementioned symptoms occur, depression is obvious to the physician.

The less obvious depression, however, is one in which the physical symptoms (not usually associated with depression) cover up the depression just as so-called agitated depression is covered up by agitation and somatic symptoms of anxiety. If the classic symptoms of depression are not present, the internist does not usually think of depression and is satisfied when no obvious organic somatic disease is present. The awareness that depression may be masked or covered up by physical symptoms that are not so-called classic symptoms has not been stressed in either the medical or the psychiatric literature.

What I have to say applies to non-psychiatrists because they are in a position to see patients whose physical symptoms in their early origin are intermingled with and may actually hide depression. Although psychiatrists have clearly described the syndrome of depression (discussing the common symptoms which occur), very little has been mentioned of the variations in the physical symptoms of depression. As internists, we see that any organ or system of organs may produce symptoms which may hide depression.

I wish to illustrate this somatization of depression, using a few case reports chosen from a private practice of internal medicine. No attempt will be made to discuss the specific dynamics in any given patient. The presenting complaints covered up the depression in all patients chosen for this report. The depression was actually more important than the presenting complaints. The physical symptoms talked about by the patients were considered together with the patient's manner, appearance, facial expressions and speech. When I was aware that depression was sometimes masked, it was possible in taking the history to make the patient aware of depression. Occasionally a life situation was mentioned, which helped to relieve the depression and with it the physical symptoms. I realize that this is not always possible. When impossible, intensive psychotherapy in the hands of a competent psychotherapist may be indicated.

Case Reports

Case 1. A 50 year old married executive with two adult children had had a severe coronary occlusion three years ago. He was a hail fellow well met who had been very successful in business and was well liked. The son of a minister, he had grown up in the West and loved the outdoors. He wanted to be a "he-man." Although he worked hard and conscientiously, he also played hard. His wife was a soft-spoken, affirmed Christian Scientist who acknowledged his acute cardiac disease but wanted him to become a Christian Scientist. Because he was dependent on her,

he paid lip service to her religious belief but would not go all the way. Following the acute illness, he became very attached to his secretary and had an affair with her. Three months following the onset of the affair he began to have vague, atypical chest pain which could be interpreted as coronary pain. All findings, including electrocardiographic evidence, failed to substantiate this interpretation. Although he continued to work, his efficiency decreased and he consulted me again because he felt he was not right. I told him that his heart was not responsible for his symptoms and that something was worrying him. He then confessed his relationship with his secretary and reluctantly admitted how guilty he felt and how depressed. This brought up the problem of his dependence. The conflict of his love for his wife (idealized mother) who gave him nothing, and his guilt about not loving the mistress who gave him so much, became apparent to him. He continues to accept the compromise of loving his wife and living with his mistress, who satisfies his dependent needs. With the relief of his guilt, due to some insight about his dependent needs, his physical symptoms lessened and, with them, his depression.

Comment: This patient developed a reactive depression with slowing of motility and symptoms of coronary insufficiency which were due to a life situation that had no immediate solution, as his wife would not give him a divorce. With decrease in guilt and acceptance of his dependent needs, his symptoms of coronary disease, which covered up his depression, were relieved.

Case 2. A 32 year old housewife and secretary, with one son from a previous marriage, had had since adolescence symptoms of severe dysmenorrhea and backache. She was sent to me because her employer felt that her work had slipped. She talked volubly about her symptoms. She had already been examined by competent gynecologists and had had one laparotomy and a cervical repair. Her backache was constant and much worse during her menses. In the course of the interview she was both preoccupied with her symptoms and self-depreciatory. Her work performance had been good up to this time and there was no apparent reason why she should depreciate herself to the extent that she did. When I asked her if she could remember when she had had her first menstrual period with dysmenorrhea, she was startled and said, "Nobody asked me that before." She said that she had been 12 years old, and that her first period occurred under peculiar circumstances. Her sister had just died in childbirth and, as was the custom, the entire family was together, mourning. The patient, who had felt that she was the least attractive of the five siblings and the most rejected, was listening to praises of the dead sister. Suddenly she felt cramps, developed a severe backache and fainted. All attention was focused on her. The family comforted and reassured her about her symptoms. After talking about this major incident, she was self-depreciatory and guilty, realizing that she had probably been having backache and dysmenorrhea ever since her first menstrual period in order to gain the attention of whomever was close to her.

Comment: The realization that the patient was depressed enabled me to direct the ventilation to a current life situation, which helped to relieve the symptom and the depression.

Case 3. A 65 year old widow who had lived with a married daughter for 15 years after her husband's death had had hypertension for years but no other complaints until she began to have severe belching. The eructations were constant and most annoying to the patient. Before seeing me she had been given a complete

physical and laboratory examination, and had been told that she was swallowing air due to nervousness. When I first saw her she seemed uncomfortable, with constant eructations. Her manner, speech and appearance all pointed to her depression. It seemed apparent that the symptom served to arouse great sympathy in her children and was for the patient a substitutive gratification. The patient had the feeling, which she finally verbalized, that she was afraid her children were going to put her out and make her live alone in a hotel. There was apparent justification for this feeling. The patient had intense hostility for her children, which she tried to conceal from both herself and the children. The patient was referred to a psychiatrist, who confirmed the diagnosis of depression and treated her with electric shock.

Case 4. A 32 year old unmarried woman consulted me because of weakness in her left arm associated with a hesitancy in her speech. These symptoms had been present for several weeks, and there had been two previous attacks of weakness in the arm and leg six and eight years earlier. Physical examination was negative except for a motor aphasia and slight muscular weakness of the muscles of the arm. On the basis of the history and findings, a diagnosis of multiple sclerosis was considered and she was sent to a neurologist, who confirmed the impression. Because I had the feeling that the patient was depressed I questioned her about her past history, and she started to cry. She became self-depreciatory and indicated that she never did or could do anything. It was pointed out that her work history had been good, that she had worked for eight years in one place and three in another as a private secretary, and that there must be other reasons for her feeling so blue. With that she confessed that she had been hiding something all her life and felt very guilty. She admitted that she masturbated and discussed the problem with tremendous feeling of guilt. When she became aware that I did not censure her, as she had anticipated I would, she felt better and the symptoms gradually disappeared. She got a new job and now, one year later, is working efficiently without symptoms. She recently became engaged to be married.

Comment: This case is another example where the symptoms of a disease (multiple sclerosis) covered up depression and where ventilation of guilt caused the symptoms of the disease and depression to disappear.

Case 5. A 29 year old unmarried female statistician had as her presenting complaint severe pain and stiffness in the neck. Although she could work, slight movement of the head increased the pain. Except for moderate spasm of the long muscles of the neck, no other positive physical or laboratory findings were noted. An x-ray of the cervical spine was also negative. Orthopedic consultation did not add to the impression of idiopathic torticollis. Again because the patient seemed more uncomfortable than the disease process warranted, and because she impressed me as being depressed, a more thorough history was indicated. It was suggested that maybe there was something she did not want to face. She said that, although her job was very good, she was lonesome in Chicago, but the other alternative was to go home to Ohio where her married sister lived in the family home. She had been attached to her father, who had been a heavy drinker and who on one occasion, when she was 12 years old, had attempted sexual play with her. She felt that to go back home was to enter the scene of a previous crime because, in her attachment to her father, she may have provoked his sexual attack. This was expressed with great feeling and her depression, which was masked by the symptoms of torticollis, seemed greater. It was suggested that she see a psychiatrist but she refused, and felt that knowing how she felt would lessen the symptom. This did happen and the patient remained at her job.

Comment: In this patient the localization of muscle spasm with pain was related to an inability to free old feelings of ambivalence towards her father and the guilt associated with the father's sexual attack. Depression which had been chronic became acute when the decision to go back home occurred. Relief of the acute depression relieved the symptom.

Case 6. A 32 year old housewife, married 10 years and mother of two children, consulted me because she was obese. She had been about 12 to 15 pounds overweight for years and wanted to lose weight. Her preoccupation with weight loss seemed out of all proportion to her slight excess weight, and I suspected an underlying depression. From the history it was obvious that the patient had compulsive eating habits. She said she had been trying unsuccessfully to diet. No specific complaints other than the obesity could be elicited. On further questioning she began to weep copiously when a discussion of her mother occurred. She felt that her mother had been very demanding of her and had had too high standards, and that she could never achieve anything her mother expected of her. She finally said that she had come to me to lose weight at her mother's insistence. The patient was the second of three children; there was a sister four years older and a brother three years younger. She felt her sister to be more competent and more easily able to meet the mother's high standards. Throughout the history taking the patient continued to cry, saying that if only she could lose weight she could satisfy at least one of her mother's demands. The physical and laboratory eraminations were all negative and the patient was advised to see a psychiatrist. She refused on the basis that her brother, then in analysis, had shown no improvement. I then gave her a low calorie diet with Dexedrine, deciding to see her once a week. In three months she had lost the suggested 15 pounds and felt wonderful. Then she went on a vacation, only to become severely depressed. She was rushed home, now willing to see an analyst. The analyst did not feel that intensive therapy was indicated or possible. The patient has since regained the weight and has continued to live in the same conflictual situation as before, with an adjustment that is socially acceptable in her environment.

Comment: In this case, although I was aware that the patient was depressed and was warding off depression by compulsive eating, I erred in treating the symptom. In general, the ego strength must be evaluated to determine if the symptom can or should be removed. The past performance of the patient in her life situation and the general chronicity of the symptoms should be measured in terms of the patient's capacity to be relieved of the symptom. In the patient just mentioned, her daily functioning is impoverished by her chronic depression, but the decision of the analyst to do no more about the obesity remained final.

Other patients have been seen with symptoms of coronary artery disease, hypertension, dizziness, so-called idiopathic headache and backache in which the symptoms have covered up depression. With the occasional relief of some emotional conflict that lessened guilt, hostility and anxiety, the physical symptoms disappeared and with it the depression. Depression in these patients has ranged in intensity and persistence from blues to deep melancholia. In some patients the symptoms of depression served as a substitutive gratification. However, the manifold and varied symptom picture of depression has to be evaluated in terms of the nature of loving and hating

impulses and fantasies at an early stage of development. The non-psychiatrist must be alert to understand that physical symptoms may cover up the syndrome. The first prerequisite in therapy in any disease process is recognition of the disease. The physician must not only be aware of depression but also must make the patient aware that he knows the patient is depressed.

In summary, case reports have been used to show that physical symptoms or disease processes can and do occur as a defense against depression, and that the internist is in a strategic position to evaluate the symptoms and occasionally to relieve the depression.

THE AGE FOR IMMUNIZATION *

By F. H. Top, M.D., F.A.C.P., *Iowa City, Iowa*

Immunization is the process of rendering or making immune, which is a function of body cells. It may occur as the result of infection naturally acquired or by the artificial stimulation of cells through injection of antigens. The act of injection of antigens is called inoculation. The word "immunization" is often used when "inoculation" is meant. Inoculation when carried out is a certainty, immunization is the anticipated result: it is a process that is hoped for. Strictly speaking, the title should read, *The Age for Inoculation,* but in the broader sense this paper also considers the age at which the process of immunization is desirable.

The age at which inoculation of antigens should take place is one of a number of facets of the general consideration of active protection against certain communicable diseases. With this in mind, the evidence for the value of inoculation, except as it bears on the question of age, will not be presented. The discussion will be limited largely to diseases for which active protection is routinely desired, namely, diphtheria, pertussis, tetanus and smallpox. Brief consideration will be given to other diseases for which active protection may be sought under certain circumstances but, as with passive protection, this involves the problem of *occasion* rather than *age* at which inoculation is desirable.

As an important aside, it is necessary to state that the optimal goal for protection of the individual and the community is to attain maximal protection against pertussis, diphtheria, tetanus and smallpox with a minimal number of injections and reactions, and to accomplish this as early in life as is practicable. However, among the above-named diseases, only pertussis occurs with any degree of regularity at present, and Cruickshank [1] states in connection with diphtheria that many parents know the disease only by name and "may require a great deal of persuasion to have children inoculated against what is to them a hypothetical danger." With a decrease in cases and carriers, applicable to diphtheria and pertussis, the length and adequacy of protection are less because of the infrequency of natural stimulation provided by contact with the organism; hence the need for more artificial stimulation. In consequence, physicians must be prepared with satisfactory reasons to persuade parents who doubt the value and safety of inoculation against the diseases mentioned.

Age at Inoculation of Single Antigens

Pertussis: It is well known that newborn and young infants have little or no inherited immunity to pertussis, and that most complications and

* From the Symposium on Pediatrics presented at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 6, 1954.

deaths occur in this group. In fact, whooping cough is serious in any child up to three years of age, often leading to protracted infection with the risk of secondary pulmonary involvement. With these facts in mind, pertussis inoculations should be given preferably within the first six months of life. How valuable and practicable is the procedure at this age? There is insufficient knowledge concerning the antigenic factors responsible for producing protection against pertussis. Evaluation of pertussis vaccines has been largely a matter of field tests, which singly have been less convincing, but which in the aggregate have indicated some protection. A model control study was conducted by Bell,[2] in which none of the participants was aware that pertussis antigen was present in certain lots of alum-precipitated diphtheria toxoid administered on the "odd" and "even" month-of-birth plan to assure adequate control and inoculated groups. Even the physician in charge of the study and observers in the field did not know whether a pertussis victim in the community had received the vaccine; this was first revealed at the conclusion of the study. The incidence of pertussis in controls was 3.45 times greater than in children who had received pertussis vaccine. Admitting the value of inoculation against pertussis, at what age should it be given?

Sako and co-workers [3] found a good response as determined by agglutination titers, and in later studies [4] reported agglutination responses in nearly 9,000 Negro children inoculated between the ages of two weeks and five years. He found no significant differences in antibody response irrespective of age at primary inoculation. Observation of 493 inoculated infants under three months of age with 438 controls of comparable age exposed to household pertussis showed an attack rate of 13.2 per cent among the vaccinated, compared to 89.7 per cent among the controls. In this study Sako showed that, in general, the pertussis attack rate in the inoculated group was inversely related to the agglutination titers, adding evidence and credence to the procedure as indicative of protection against pertussis. Others, notably Sauer,[5] Adams et al.[6] and Halpern and Halpern,[7] have reported production of immunity against the disease as measured by antibody titers or skin tests. Confirmation has also come from reports of pertussis antigens incorporated in multiple antigen preparations and given to infants under three months of age by di Sant'Agnese,[8] Bradford and associates [9] and Peterson and Christie.[10] From the foregoing evidence it appears that it is feasible and worth while to inoculate infants under the age of three months (as early as four to six weeks old) and to expect a protective level of better than 75 per cent.[10] Many investigators agree with Sauer,[11] however, that a poorer antibody response occurs in early infancy than in later infancy or early childhood.

To guard against relapse of protection in infants given pertussis vaccine, booster doses are advocated at one year, and confirmation of value has been demonstrated by Sako,[3] di Sant'Agnese [8] and Kendrick and co-workers.[12] Di Sant'Agnese [8] and Peterson and Christie [10] found greater antigenic re-

sponse following booster doses given to infants first inoculated between the ages of six and 12 months. However, as Miller [13] indicates, less good antigenic response under age six months must be weighed against the hazard of contracting pertussis at this period, and he inclines to the use of pertussis vaccine in early infancy, particularly when the physician knows that pertussis is prevalent in his community.

Pertussis vaccine may be given as early as four to six weeks of age with assurance of protection in most infants injected with alum-precipitated vaccine containing 60 to 100 billion killed organisms divided into three or four doses. Superior agglutinin titers result from the use of the alum-precipitated compared to the fluid vaccine. Reactions to injection of pertussis vaccine are minimal, particularly at such an early age.

Diphtheria: Although the occurrence of diphtheria has diminished markedly in the past three decades, World War II experience indicates that in some areas where inoculation against diphtheria was practiced intermittently, poorly or not at all, large outbreaks occurred. In fact, in a few instances where the immune level of the population was above the accepted minimum supposedly adequate for protection, epidemics occurred during wartime in Denmark, as reported by Ipsen.[14] Studies in the United States indicate that Schick-positive rates in various adult groups vary from 29 to 82 per cent, and similar figures have come from studies in other countries.[15] In spite of a challenge to its effectiveness by some recent foreign reports, it is safe to say that adequate inoculation procedures against diphtheria results in 85 to 95 per cent of protection as indicated by Schick's test or blood titration levels.

When diphtheria was prevalent, a large proportion of newborn infants were protected for periods of up to six months by placental transfer of maternal antibodies. With so many mothers now Schick-positive, it is necessary to inoculate at an earlier age, for infants of susceptible mothers are not immune. However, it has long been recognized that the presence of maternally derived antibodies interferes with neonatal inoculation against diphtheria. Cooke [16] has recently confirmed this. Careful consideration must therefore be given to the age at which diphtheria antigen is offered.

In a community where a goodly number of individuals, including adults, are protected, the primary dose of diphtheria toxoid should be given at age six months whereas evidence of a high Schick-positive rate among adults would make first inoculation at age three months more desirable. Whenever given, two doses of alum-precipitated toxoid should be administered at monthly intervals. Booster doses should be given at one year of age if the primary injection occurred at age three months, or at 18 months of age if first injected at six months; another booster injection should be given just prior to entry in preschool or kindergarten. Reactions to injections of diphtheria toxoid are minimal in infancy. Further booster doses may be given if an outbreak of diphtheria occurs in school or neighborhood. Some

advocate booster injections at three year intervals, but these should not be continued after age 12 years.

Tetanus: The effectiveness of tetanus toxoid in military personnel was amply demonstrated in World War II.[17] The routine use of tetanus toxoid has been questioned, but Press,[18] analyzing the evidence for and against, re-emphasizes the danger of contracting tetanus from unrecognized or minor injuries in addition to severe trauma. He collected 982 tetanus cases classified by degree of injury and found 15 per cent of the group developed from "trivial" involvement, while 34.5 per cent were ascribed to the classification "injury unknown."

It is apparent that protection against tetanus is worth while, and inoculation in infancy is most desirable. Tetanus toxoid is well tolerated, reactions are infrequent and it is an effective immunizing agent. Primary inoculations may be given at any time, for age is not a factor in antigenic response. Alum-precipitated toxoid may be given in two doses, spaced one month apart, at any time during the first year of life, with resulting high titers to be anticipated. Booster doses should be given at three year intervals and after injury. Booster or recall doses result in a very satisfactory antibody rise within two and one-half to five years after the primary inoculation, as demonstrated by McBryde and Poston [19] and by Volk and associates.[20] Miller and co-workers [21] found that fluid toxoid results in a titer rise in most subjects by the fourth day, and in all by the fifth day. Miller and Ryan [22] emphasize that the rate of recall is lengthened if more than four years have elapsed since basic inoculation or booster injection. In the instance of compound fractures, massive contamination and the like, Miller [23] gives 5,000 units of tetanus antitoxin in addition to a booster dose of fluid toxoid. This combination is of value only to individuals previously inoculated with tetanus toxoid.

Smallpox: The incidence of smallpox continues to decline in the United States, but outbreaks in the past decade in San Francisco,[24] Seattle [25] and New York City [26] should be a reminder that smallpox is an ever present threat unless vaccination is continued assiduously. England has had similar and more frequent outbreaks in the same period of time. Primary vaccination against smallpox should be accomplished in childhood, preferably between the sixth and twelfth months of life. It is often done at the time the last diphtheria toxoid or the last multiple antigen injection is given. The multiple pressure method of administration should be used, and if potent vaccine is used few failures will result. In the absence of an active take, vaccination should be repeated until a take appears. Continued negative primary reactions do not indicate immunity unless an individual has had smallpox.

Other Diseases: Inoculation with *scarlet fever* antigens is not recommended for infants and children unless they reside in institutions, in which instance the procedure is considered advisable by some. Likewise, *typhoid fever* inoculations are not recommended except for children and adults who

reside in or contemplate travel to endemic areas. Active immunization against *Rocky Mountain spotted fever* is suggested at all ages only if residence is contemplated in certain heavily tick-infested areas in Montana, where a severe form of the disease prevails. The disease is milder elsewhere in the United States, and presence of ticks in such areas does not necessitate inoculation, for the newer antibiotics are very effective in the treatment of this disease. Routine inoculation against *influenza* is not recommended for children or adults unless to them, as weaklings, an attack of the disease would be hazardous. At best, immunity appears to be short-lived, and the vaccine used must contain the strain of virus to which the individual will be exposed. In contrast to adults, infants and young children may react rather severely to influenza vaccine, and some investigators feel the antibody response is inferior. Although *mumps* vaccine is available commercially, it is not recommended as a routine procedure. Inoculation of adults prior to the occurrence of an outbreak has demonstrated lower attack rates among the inoculated.[27, 28] Much additional information is necessary with respect to duration of protection and other factors before inoculations can be recommended for children.

Age at Inoculation of Multiple Antigens

Inoculation of infants and children with preparations containing more than one antigen has increased in favor during the past decade. French investigators [29, 30] reported the use of so-called combined vaccination in man as early as 1934, but it was somewhat later before such preparations were used in the United States. Early combinations administered in this country were diphtheria-tetanus,[31] diphtheria-pertussis [32] and diphtheria-tetanus-pertussis.[33] In addition, four and five antigen preparations have been studied by Volk [34] to determine their safety and effectiveness. The most commonly used combination is the diphtheria-tetanus-pertussis preparation (D-T-P).

When the use of single antigens was considered it was found desirable to inoculate as early as possible against pertussis, and sufficient protection resulted when the initial injection was given between the second and third month, even though greater protection occurred when injections were carried on after the sixth month. The response to diphtheria inoculation appeared to be less good, particularly where partial protection had been conveyed by mothers to their newborn infants. However, Bell [2] found that the combination of pertussis and diphtheria resulted in enhancement of protection against diphtheria by the presence of pertussis antigen; the opposite effect—diphtheria antigens having an adjuvant effect on development of pertussis immunity—did not obtain. Tetanus can be given at any time. The studies of Fleming et al.,[35] di Sant'Agnese,[36] Volk,[34] Bradford et al.[9] and Christie and Peterson,[10] among others, add weight to the findings.

In general, adequate antibody levels are produced against diphtheria, pertussis and tetanus by multiple antigen preparations given to very young

infants, but the first two antigens produce a greater effect at ages above six months. However, a booster dose of the multiple antigen preparation given within six months of the first injection gives an equally good response in infants first inoculated at ages two months and six months, but booster response to pertussis antigen is definitely superior in the older infant group. These findings are demonstrated particularly in the studies of Fleming and associates [88] and di Sant'Agnese.[86]

Inoculation schedules utilizing multiple antigens for protection of infants against diphtheria, tetanus and pertussis have been formulated by, among others, di Sant'Agnese,[6] Peterson and Christie [100] and Miller.[33] Di Sant'-Agnese (table 1) feels that inoculations of triple antigens should be started not earlier than three months of age until further studies have demonstrated better protection at earlier ages. He investigated the protection levels of infants started at one week of age with triple vaccine given at monthly

TABLE 1

Age at Inoculation

Method of di Sant'Agnese*

Injection	Age (months)	Preparation	Amount (c.c.)
1	3	Triple vaccine†	0.5
2	4	Triple vaccine†	1.0
3	5	Triple vaccine†	1.0
4	18	Triple vaccine†	0.5

* di Sant'Agnese: Pediatrics **3**: 333 (Mar.) 1949.

† Triple combined antigen containing 20 billion *H. pertussis* organisms per cubic centimeter and alum. hydroxide-adsorbed tetanus and diphtheria toxoids.

intervals, for three doses with "older" infants begun at three months of age, giving the same product for three doses spaced one month apart. On the basis of his observations—that protection increases with increasing age of the infant in months for both diphtheria and pertussis—he prefers to begin inoculations no earlier than at age three months. As stated previously, the age at which tetanus toxoid is administered does not alter antibody response appreciably.

Christie and Peterson (table 2) feel that protection afforded by earlier injections with all three antigens is sufficient to warrant first inoculation before the age of three months. They begin inoculations at age four to six weeks with a single pertussis antigen containing 20 to 40 billion organisms, followed by the first dose of diphtheria-tetanus-pertussis mixture at eight to 10 weeks of age, with repeat injections of the same triple antigen at 14 to 16 weeks and at 20 to 22 weeks, and booster doses at 18 months and five years. Di Sant'Agnese and Miller begin with a triple antigen preparation, Miller at four to six weeks, di Sant'Agnese one month later. Both give

TABLE II

Age at Inoculation

Method of Christie and Peterson*

Injection	Age	Preparation	Amount
1	4–6 weeks	Pertussis vaccine	20 billion *H. pert.*
2	8–10 weeks	Pertussis vaccine	30 billion *H. pert.*
		Diphtheria toxoid	30–40 Lf.
		Tetanus toxoid	30–50 Lf.
3	3.5–4 months	Triple vaccine	Same as 2nd injection
4	5 months	Triple vaccine	Same as 2nd injection
5	18 months	Triple vaccine	½ of 2nd injection
6	5 years	Triple vaccine	½ of 2nd injection

* Christie, A., and Peterson, J. C.: Am. J. Dis. Child. 81: 518 (Apr.) 1951.

two additional doses at monthly intervals, with a booster dose at age 18 months.

Miller feels that a single schedule of inoculations does not fit all conditions. The degree of immunity in one's community should be known and a program based on this information be arranged. In many communities today, 50 per cent or more of adults are Schick-positive. On this basis, Miller tests mothers of one month old infants to determine their Schick status. If the mother is Schick-positive he uses Schedule A (table 3), and if Schick-negative, Schedule B (table 4). With the mother Schick-positive, inoculations of a triple vaccine are begun at ages of from four to eight weeks, giving 0.5 c.c. of the mixture and following the second dose at an interval of one month and the third dose at an interval of three months. Booster doses are given at 18 months and thereafter every three years to 10 years of age and, if necessary thereafter, a skin test is performed utilizing 1/100 c.c. of plain diphtheria toxoid to test sensitivity before an additional booster dose is given. On injury, a dose of plain tetanus toxoid is administered

TABLE III

Age at Inoculation

Method of Miller*

A. *Infants of Schick-Positive Mothers*

Injection	Age	Preparation	Amount (c.c.)
1	4–8 weeks	Triple vaccine†	0.5
2	8–12 weeks	Triple vaccine†	0.5
3	20–24 weeks	Triple vaccine†	0.5
4	18 months	Triple vaccine†	0.5
5	3-yr. intervals	Triple vaccine†	0.25

* Miller, J. J., Jr.: Pediatrics 3: 126 (Jan.) 1951.

† Alum-precipitated or alum. hydroxide adsorbed diphtheria and tetanus toxoid, containing 30 billion *H. pertussis* organisms per cubic centimeter.

TABLE IV

Age at Inoculation

Method of Miller*

B. *Infants of Schick-Negative Mothers*

Injection	Age	Preparation	Amount (c.c.)
1	2 months	Pertussis vaccine†	0.5
2	3 months	Pertussis vaccine†	0.5
3	5 months	Triple vaccine‡	0.5
4	7 months	Triple vaccine‡	0.5
5	10 months	Triple vaccine‡	0.5
6	3-yr. intervals	Triple vaccine‡	0.25

* Miller, J. J., Jr.: Pediatrics **3**: 126 (Jan.) 1951.
† Simple precipitated *H. pertussis* vaccine.
‡ Alum-precipitated or alum. hydroxide adsorbed diphtheria and tetanus toxoid containing 30 billion *H. pertussis* organisms per cubic centimeter.

and, if the injury is severe, 5,000 units of tetanus antitoxin are given additionally. Miller feels that protection against tetanus should be renewed every three years of life.

In the instance of the Schick-negative mother, Miller gives two doses of simple precipitated *Hemophilus pertussis* vaccine at ages two and three months, and follows this at ages five, seven and 10 months with 0.5 c.c. of a triple vaccine incorporating pertussis, diphtheria and tetanus antigens. Booster doses are given as outlined under discussion of Schedule A.

SUMMARY

At the present time inoculation of single antigens need not be given except under special circumstances, such as using pertussis antigen at one or two months of age.

Since multiple antigen preparations generally produce little more reaction than antigens used singly, and antibody production is equal to or better because of an adjuvant effect, as in the instance of diphtheria and tetanus in the presence of pertussis antigen, multiple antigen preparations containing these antigens should be employed beginning not later than three months of age, and earlier if the occurrence of pertussis, diphtheria or both so warrants.

Smallpox vaccination may be carried out at any time during the first year of life, but preferably on the last injection of the full course of three or four injections of a multiple antigen preparation.

No absolute schedule can be followed under all circumstances, particularly in view of the differences in immunity status of communities, and because field studies have lacked adequate population units at risk to pertussis and diphtheria under test conditions other than mild endemic occurrence. Further investigations are needed to elucidate the problems involved.

BIBLIOGRAPHY

1. Cruickshank, R.: Pros and cons of immunization, Brit. M. J. **1**: 212 (Jan. 26) 1952; and **1**: 268 (Feb. 2) 1952.
2. Bell, J. A.: Pertussis immunization: use of two doses of alum-precipitated mixture of diphtheria toxoid and pertussis vaccine, J. A. M. A. **137**: 1276, 1948.
3. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J.: Early immunization against pertussis with alum precipitated vaccine, J. A. M. A. **127**: 379 (Feb. 17) 1945.
4. Sako, W.: Studies on pertussis immunization, J. Pediat. **30**: 29, 1947.
5. Sauer, L. W.: Whooping cough: prevention and treatment, M. Clin. North America **30**: 45, 1946.
6. Adams, J. M., Kimball, A. C., and Adams, F. H.: Early immunization against pertussis, Am. J. Dis. Child. **74**: 10, 1947.
7. Halpern, S. R., and Halpern, D.: Early whooping cough immunization, J. Pediat. **33**: 43, 1948.
8. Di Sant'Agnese, P. A.: Combined immunization against diphtheria, tetanus and pertussis in newborn infants. I. Production of antibodies in early infancy, Pediatrics **3**: 20 (Jan.) 1949. II. Duration of antibody levels. Antibody titers after booster dose. Effect of passive immunity to diphtheria on active immunization with diphtheria toxoid, Pediatrics **3**: 181 (Feb.) 1949. III. Relationship of age to antibody production, Pediatrics **3**: 333 (Mar.) 1949.
9. Bradford, W. L., Day, E., and Martin, F.: Humoral antibody formation in infants aged one to three months injected with a triple (diphtheria-tetanus-pertussis) alum precipitated antigen, Pediatrics **4**: 711 (Dec.) 1949.
10. (a) Peterson, J. C., and Christie, A.: Immunization in the young infant: response to combined vaccines, I-IV, Am. J. Dis. Child. **81**: 483 (Apr.) 1951.
    (b) Christie, A., and Peterson, J. C.: Immunization in the young infant. Response to combined vaccines, V, Am. J. Dis. Child. **81**: 501 (Apr.) 1951.
    (c) Peterson, J. C., and Christie, A.: Immunization in the young infant. Response to combined vaccines, VI-X, Am. J. Dis. Child. **81**: 518 (Apr.) 1951.
11. Sauer, L. W.: Age factor in active immunization against whooping cough, Am. J. Path. **17**: 719, 1941.
12. Kendrick, P. L., Eldering, G., and Thompson, M.: Reinforcing or "booster" injection of pertussis vaccine in previously immunized children of kindergarten age: pertussis field series V, Am. J. Dis. Child. **72**: 382, 1946.
13. Miller, J. J., Jr.: Immunization procedures in infancy, Postgrad. Med. **9**: 160 (Feb.) 1951.
14. Ipsen, J.: Circulating antitoxin at onset of diphtheria in 425 patients, J. Immunol. **54**: 325, 1946.
15. Edsall, G.: Active immunization, New England J. Med. **241**: 18–26, 60–70, 99–107 (July 7, July 14 and July 21) 1949.
16. Cooke, J. V.: Antibody formation in early infancy against diphtheria and tetanus toxoids, J. Pediat. **33**: 141, 1948.
17. Long, A. P., and Sartwell, P. E.: Tetanus in United States Army in World War II, Bull. U. S. Army M. Dept. **7**: 371, 1947.
18. Press, E.: Desirability of routine use of tetanus toxoid, New England J. Med. **239**: 50, 1948.
19. McBryde, A., and Poston, M. A.: Immunization with tetanus toxoid: persistence of antitoxin and effect of stimulating doses of alum-precipitated tetanus toxoid after five-year period, J. Pediat. **28**: 692, 1946.
20. Volk, V. K., Top, F. H., and Bunney, W. E.: Reinoculation with multiple antigen preparations of free-living children previously inoculated with multiple antigen preparations, Am. J. Pub. Health **43**: 821 (July) 1953.

21. Miller, J. J., Jr., Ryan, M. L., and Beard, R. R.: Speed of secondary immune response to tetanus toxoid with review of war reports and observations on simultaneous injection of toxoid and antitoxin, Pediatrics **3**: 64, 1949.
22. Miller, J. J., Jr., and Ryan, M. L.: Combined active-passive reimmunization against tetanus in previously immunized individuals: experimental and clinical evidence, J. Immunol. **65**: 143 (Aug.) 1950.
23. Miller, J. J., Jr.: Round table discussion: immunology in practice of pediatrics, Pediatrics **7**: 118 (Jan.) 1951.
24. Geiger, J. C.: Smallpox situation in San Francisco, J. A. M. A. **130**: 1261, 1946.
25. Palmquist, E. E.: 1946 smallpox experience in Seattle, Canad. J. Pub. Health **38**: 213, 1947.
26. Weinstein, L.: Outbreak of smallpox in New York City, Am. J. Pub. Health **37**: 1376, 1947.
27. Habel, K.: Vaccination of human beings against mumps: vaccine administered at the start of an epidemic, Am. J. Hyg. **54**: 295 (Nov.) 1951.
28. Cabasso, V., Ruegsegger, G. K., and Cox, H. R.: The immunologic response of children to the injection of chick embryo propagated mumps virus vaccine as measured by the complement-fixation test, J. Lab. and Clin. Med. **35**: 771 (May) 1950.
29. Tanon, L., and Cambessedes, H.: Combined vaccinations, Rev. franç. de puériculture. **2**: 298 (Nov.) 1934.
30. Ramon, G.: Immunization with multiple antigens (associated vaccination). Theoretical and practical considerations, Rev. d'immunol. **2**: 415, 1936.
31. Bigler, J. A., and Werner, M.: Active immunization against tetanus and diphtheria in infants and children, J. A. M. A. **116**: 2355 (May 24) 1941.
32. Kendrick, P. L.: A field study of alum-precipitated combined pertussis vaccine and diphtheria toxoid for active immunization, Am. J. Hyg. **38**: 193 (Sept.) 1943.
33. Lapin, J. H.: Combined immunization of infants against diphtheria, tetanus and whooping cough, Am. J. Dis. Child. **63**: 225 (Feb.) 1942.
34. Volk, V. K.: Safety and effectiveness of multiple antigen preparations in a group of free-living children, Am. J. Pub. Health **39**: 1299, 1949.
35. Fleming, D. S., Greenberg, L., and Beith, E. M.: Use of combined antigens in immunization of infants, Canad. M. A. J. **59**: 101, 1948.
36. Di Sant'Agnese, P. A.: Combined immunization against diphtheria, tetanus and pertussis in children over three months of age, including evaluation of effectiveness of two immunizing agents, J. Pediat. **31**: 251, 1947.

CARDIAC AND NON-CARDIAC CHEST PAIN: A STATISTICAL STUDY OF "DIAGNOSTIC" CRITERIA *

By Arthur M. Master, M.D., F.A.C.P., Harry L. Jaffe, M.D., and Leon Pordy, M.D., *New York, N. Y.*

The increasing frequency of chest pain, due to the lengthening of the life span, and the importance of differentiating between chest pain of cardiac and non-cardiac origin cannot be overemphasized. Chest pain of cardiac origin is usually associated with coronary artery disease. Heberden [1] first described angina pectoris in 1772, and until recently little had been added to his detailed observations. During the past several decades, however, the diagnosis of coronary disease has been greatly facilitated. As a result, many mild and atypical cases can now be discovered.[2] This explains in large part the present increase in the incidence of coronary disease, and has broadened our understanding of angina pectoris. The differential diagnosis between cardiac and non-cardiac pain, hitherto often based on the history of the attack, has now become less sharp, and at times is very difficult.

The criteria usually employed in differentiating between angina and non-cardiac chest pain are:

	Angina Pectoris	Non-Cardiac
Onset	On effort or emotion	Spontaneous
Location	Substernal	Apical
Duration	Less than 5 minutes	Prolonged
Type	Constricting	Sticking, aching
Relief by nitroglycerin	Prompt	None
Radiation	Commonly to left arm	Uncommon

Occasional reports in the literature tend to show that these criteria are not pathognomonic. In a study of patients with angina pectoris, Harrison [3] found the pain to be substernal in only half the cases. It was mild or minimal in one out of every two patients; not infrequently it was described as aching or burning. It was "typically" constrictive or "pressing" in only 50 per cent. He found the recumbent position to be a frequent precipitating factor of anginal pain, and noted that patients with angina of effort often also experience pain spontaneously. In addition, he found that in 10 per cent of patients the pain occurred in the absence of any effort.

Parkinson [4] stated that radiation of the pain to the left arm is not characteristic of angina pectoris, since it occurs in hiatus hernia and in esophageal, pleural and spinal disease. He also found nitroglycerin to be of minor differential diagnostic importance, since it does have a beneficial effect

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York.

in pain of psychic origin. Relief by nitroglycerin of non-cardiac pain, including the pain of spondylitis and intestinal spasm, has been noted by other authors also.[5-10] It seems that the drug was used many years ago to relieve brachial neuritis and fibrositis.[11]

CHEST PAIN QUESTIONNAIRE

Name.....Date.....History No.....

Sex.....Age.....Occupation.....

COMPLETED BY.....(patient) or.....M.D.

INSTRUCTIONS: Please FILL IN EVERY SPACE ON THIS FORM, using check mark (V) for "yes" and zero (0) for "no." LEAVE BLANK ONLY IF UNKNOWN.

DURATION of chest pain or pressure.....years.....months.

TYPE:

Squeezing	Sticking
Constricting	Gnawing
Strangling	Aching
Compressing	Vise-like
Burning	Choking
Heaviness	Tightness
Pressure	Knife-like
Boring	Discomfort
Dull	Others

LOCATION OF PAIN OR PRESSURE:

Substernal (under breast bone)
Precordial (over heart in left lower chest)
Pit of Stomach
Back
Chest—entire.....left.....right.....
Other

DURATION OF PAIN OR PRESSURE: each attack.

Up to 1 minute
1 to 2 minutes
2 to 5 minutes
5 to 10 minutes
10 minutes to 1 hour
Over 1 hour
Continuous

FREQUENCY OF ATTACKS:

More than once a day
Once a day
Few times a week
Few times a month
Rare—Under once a month

RADIATION OF PAIN OR PRESSURE:

None
Back
Shoulder—both.....left.....right.....
Arm —both.....left.....right.....
Hand —both.....left.....right.....
Jaw
Neck
Other

ONSET:

Effort
Walking
Climbing
Emotion
Meals
Walking after meals
Cold
Walking in the cold
Walking against the wind
Spontaneous (no apparent cause)
Smoking
Intercourse
Fatigue
Lying down
Other

RELIEF OF PAIN OR PRESSURE:

	Relieves? *Yes* How many minutes?	*No*	*Not used*
Nitroglycerin			
Whiskey			
Rest			
Belching			
Spontaneous			
Other			

TOBACCO: .....Cigarettes / Cigars.....daily.

E.C.G.
"2-step"
"2-step"

B.C.G.—Normal.....Abnormal.....

REMARKS:

FIG. 1.

Conner found that the pain occurring in a cardiac neurosis may have all the characteristics usually ascribed to anginal pain.[12] Pain induced by effort and cold has been observed in spondylitis [7, 13] and in functional disorders.[14, 15] Despite these findings, the reproduction of pain by *specific* effort has proved to be of great diagnostic value in cases of angina pectoris.[16]

Although references to this subject in the literature are rather scanty, we had been impressed by the numerous exceptions to each one of the criteria usually accepted for differentiating between cardiac and non-cardiac pain. In view of the vital importance of this problem today a statistical study of the subject was deemed essential.

A questionnaire (figure 1) was drawn up and a detailed history was obtained from 200 consecutive private patients complaining of chest pain. Half the patients had coronary disease, with an abnormal resting electrocardiogram. The other half were considered to be free of heart disease, because of a normal resting electrocardiogram and a negative double "2-step" test. About 80 of these suffered from some functional disturbance; in the majority, the diagnosis was neurosis; in the remainder, neurocirculatory asthenia, uncomplicated hypertension or hypotension, or paroxysmal arrhythmia was present. The remaining 20 cases were found to have some type of arthritis, gall-bladder disease, peptic ulcer or hiatus hernia. The diagnosis of non-cardiac disease was confirmed by the fact that none of these patients had developed coronary insufficiency or occlusion during a four year period of observation.

As was expected, the majority of the patients with coronary disease were male and over the age of 50. We were surprised, however, to find that the great majority of the non-cardiac patients were male also, and that almost one-half were 50 years of age or older.

Considerable care was required in eliciting a description of the *type of pain* experienced by patients with coronary disease. They often had difficulty in describing their discomfort. Not uncommonly, they strongly denied having "pain" at all. Figure 1 reveals the diversity of terms which they used. The commonest were pressure, constricting, aching, tightness, choking, sticking and burning (table 1). Other descriptive terms were heavi-

TABLE I

Chest Pain—Type

	100 Coronary Disease	100 Functional
Pressure*	61	52
Constricting†	42	17
Aching‡	41	45
Tightness	32	9
Choking	14	6
Sticking§	13	14
Burning	10	6

* Pressure and heaviness.
† Constriction, squeezing, strangling, compressing, vise-like.
‡ Aching, dull, gnawing, discomfort, throbbing.
§ Sticking, knife-like.

ness, compressing, squeezing, vise-like, gnawing, throbbing, discomfort and knife-like (table 2). It is not uncommon for a patient to complain of more than one type of pain.

The most common complaint in both the cardiac and non-cardiac patients was a sensation of pressure or heaviness; it occurred in half the patients in each group. "Tightness" was distinctly more common in the patients with coronary disease, and "constriction" was also definitely more frequent. Among the functional cases, "aching" was almost as common as "pressure," but it was also a frequent complaint in the cardiac cases (41 per cent), as

TABLE II

Chest Pain—Type
100 Coronary Disease—100 Functional

	C	F		C	F
Constricting:			*Aching:*		
Constricting	15	6	Aching	16	19
Compressing	12	5	Discomfort	10	4
Squeezing	7	3	Gnawing	6	7
Vise-like	6	1	Throbbing	5	5
Strangling	2	1	Dull	4	10
(Boring)	0	1		—	—
	—	—		41	45
	42	17			
Sticking:			*Pressure:*		
Sticking	8	6	Pressure	43	35
Knife-like	5	8	Heaviness	18	17
	—	—		—	—
	13	14		61	52

Harrison had found.[3] "Choking" and "burning" were somewhat more common in the cardiac cases; "sticking pain" occurred almost as often in these as in the non-cardiac patients.

It is thus clear that the character of the chest pain in itself is not a criterion for differentiating cardiac from non-cardiac pain. Both types of pain are most commonly experienced as "pressure." While it is true that a sensation of "tightness" or "constriction" favors the diagnosis of angina, such pain is not infrequent in non-cardiac conditions. Similarly, an "aching" or "dull" pain suggests its non-cardiac origin, but it is common in patients with coronary disease also, often in association with constricting pain.

TABLE III

Chest Pain—Duration

	100 Coronary Disease	100 Functional
Substernal	41	23
Precordial	30	44
Chest		
Entire	22	13
Left	19	29
Right	1	1
Back	8	4
Epigastrium	4	1

TABLE IV

Chest Pain—Onset

	100 Coronary Disease	100 Functional
Effort	91	34
Emotion	53	25
Spontaneous	31	66
Meals	25	10
Cold	23	3
Coitus	13	2

As was expected, the pain in almost half the patients with coronary disease was *substernal,* but 23 per cent of the functional cases also localized their pain in this region (table 3). Precordial pain was more frequent in the functional cases (44 per cent), but it occurred in 30 per cent of the cardiac patients. Although back pain was rather infrequent in this series, it was twice as common in the cardiac cases as in the functional.

Like the type of pain, therefore, the location of the pain is not a good differential diagnostic criterion between cardiac and non-cardiac conditions.

In about half of both groups of patients, the pain did not radiate. When radiation did occur, it was rather similar in both groups. The radiation of the pain, therefore, is also not an aid in distinguishing between pain of cardiac and of non-cardiac origin.

TABLE V

100 Coronary Disease—Chest Pain and Effort

No effort at all	9
Walking and any other effort	68
No walking but other effort	23

Only on climbing 9, exertion after meals 1, driving car 1, walking against wind 1, overworking 1, bending 1, moving chair 1, talking fast 1, strain and effort 1, effort in general 2, climbing and exertion after meals 2, climbing, exertion after meals and walking against wind 1, exertion after meals and walking against wind 1—total 23.

Although anginal pain is generally assumed to bear a constant relation to *effort,* this was true in only 90 per cent of our patients with coronary disease (table 4). However, the pain was occasionally induced only by some very specific exertion or combination of activities (table 5), not necessarily severe. Anginal pain frequently was associated with emotional disturbances (53 per cent). It occurred entirely spontaneously in nine patients. In 32 patients, walking never evoked the anginal syndrome. These patients walked at an average rate, or even faster. However, patients with coronary disease often are afraid to walk at all, or move slowly when they do walk. Of course, it was not uncommon for patients to experience pain both on effort and spontaneously. Anginal pain was often induced by meals, cold and coitus, especially the latter two. Although two thirds of the functional patients developed pain spontaneously, as was expected, it was surprising to find that 34 per cent also related their pain to effort. In only 25 per cent of these non-cardiac cases was it induced by emotion.

TABLE VI

Chest Pain—Relief

	100 Coronary Disease	100 Functional
Nitroglycerin—*Used*	79	27
a. Relief	62 (79%)	10
b. Relief but reaction	2	1
c. Gradual relief (5–10 minutes)	1	1
d. Questionable relief	5	2
e. No relief	9 (11%)	13
Nitroglycerin—*Not Used*	21	73
Rest	41	18
Whiskey	11	3
Belching	7	4
Spontaneous	8	31

It is thus clear that there are numerous exceptions to the rule that anginal pain is related to effort, and that functional pain occurs spontaneously.

The effectiveness of nitroglycerin in relieving chest pain also failed, as a criterion to distinguish between anginal and non-cardiac conditions, in a significant number of cases (table 6). It did not relieve pain in at least one out of five cardiac patients, and did in at least 10 out of 27 patients with functional pain. This high proportion may be reduced in a larger series of cases, but it is obvious that nitroglycerin not infrequently relieves functional pain also.

DISCUSSION

A considerable number of cases of anginal and functional pain are atypical insofar as any single feature, ordinarily considered characteristic of either type, is concerned. Furthermore, many cardiac patients do not exhibit any of the characteristic pain patterns; consequently, one should not exclude the diagnosis of angina pectoris because they are not present. This is well illustrated by an analysis of the character of the pain. One-half the cardiac patients complained of a sensation of "pressure," rather than a "constricting" pain. Yet "pressure" in the chest, of itself, is not diagnostic of cardiac pain, since half of the functional cases presented a similar complaint. The other generally accepted "typical" features of angina pectoris (substernal location, onset with effort and relief by nitroglycerin) are also not diagnostic criteria. Any one of these criteria may be absent in angina pectoris and be present in functional pain.

Nevertheless, it must be emphasized that a careful history usually does enable one to differentiate the two types of pain. The patient with angina pectoris experiences the pain much more frequently on effort than at rest, whereas the converse is true in cases of functional pain. Pain induced only by effort, emotion or cold is probably cardiac in origin. In angina pectoris, the pain is apt to be relieved promptly and completely by nitroglycerin, whereas in non-cardiac disease the effect on the pain is slower and incomplete. Yet, in any specific instance, the diagnosis may defy the keenest

clinical acumen and depend on a complete examination and on long continued observation.

Summary

The diagnosis of chest pain has always been an important medical problem. With the increasing life span and the resultant increase in the incidence of coronary heart disease, anginal pain has become even more common than heretofore. Moreover, pain in the chest is frequently non-cardiac in origin. This type of pain is chiefly the result of a neurogenic disturbance, but it may be due to other conditions such as spondylitis, arthritis, neuritis, fibrositis or myositis, hiatus hernia, gall-bladder disease, peptic ulcer and chronic lung disease.

Chest pain has usually been considered cardiac in origin if (1) it was induced by effort, (2) its location was substernal, (3) it was constricting or oppressive in type, (4) it radiated into the left shoulder or arm, (5) it was of short duration, (6) it was relieved by nitroglycerin.

Non-cardiac chest pain, on the other hand, was assumed to have the following characteristics: (1) it occurred at rest, (2) its location was in the left chest, (3) it was aching in quality, (4) it did not radiate, (5) it was of long duration, and (6) it was not relieved by nitroglycerin.

Although the majority of cases can be differentiated on the basis of these criteria, a large number of exceptions occurs. Since many physicians often rely on any one of the criteria for diagnosis, it appeared advisable to make a statistical study to determine the diagnostic value of each criterion.

We investigated 100 patients with coronary disease and angina pectoris, all with abnormal electrocardiograms, and 100 patients with non-cardiac pain.

We found that the exceptions to the pathognomicity of the six criteria ranged from 15 to 40 per cent. For example, in one fourth of the non-cardiac cases the pain was substernal, and in one third it was associated with effort. It was relieved by nitroglycerin in more than 10 of the 27 of these patients who employed this drug repeatedly. On the other hand, in a third of the patients pain of cardiac origin was located in the precordial area or in the left chest, rather than in the substernal region. It occurred at rest as well as on effort in 31 per cent, and was not relieved by nitroglycerin in 10 to 15 per cent.

None of the six characteristics hitherto accepted should be used alone to differentiate between cardiac and non-cardiac chest pain. However, when three or more of the characteristics of either cardiac or non-cardiac pain are present, a definite diagnosis can usually be made.

BIBLIOGRAPHY

1. Heberden, W.: Some account of a disorder of the breast, Vol. 2, 1772, Med. Trans., Royal College of Physicians, London, p. 59.
2. Master, A. M., Jaffe, H. L., and Pordy, L.: Chest pain—cardiac vs. non-cardiac, M. Clin. North America, in press.

3. Harrison, T. R.: Clinical aspects of pain in the chest. I. Angina pectoris, Am. J. M. Sc. **207**: 561, 1944.
4. Parkinson, J.: Cardiac symptoms, Ann. Int. Med. **35**: 499, 1951.
5. Smith, J. R., and Kountz, W. B.: Deformities of the thoracic spine as a cause of anginal pain, Ann. Int. Med. **17**: 604, 1942.
6. Binger, C.: Psychological phenomena in cardiac patients, Bull. New York Acad. Med. **24**: 687 (Nov.) 1948.
7. Davis, D., and Ritvo, M.: Osteoarthritis of the cervicodorsal spine (radiculitis): similarity to coronary artery disease. Clinical and roentgenologic findings, New England J. Med. **238**: 857, 1948.
8. Sprague, H. B.: Conditions commonly mistaken for coronary occlusion and angina pectoris, Am. Pract. **4**: 238, 1948.
9. Friedberg, C. K.: Diseases of the heart, 1949, W. B. Saunders Company, Philadelphia, pp. 353, 378.
10. Allison, D. R.: Pain in the chest wall. Similarity to heart disease, Brit. M. J. **1**: 332 (Feb. 11) 1950.
11. Clinical memoranda: Cure or relief of cases misdiagnosed "angina of effort," Brit. M. J. **2**: 891, 1938.
12. Conner, L. A.: The psychic factor in cardiac disorders, J. A. M. A. **94**: 447, 1930.
13. Schott, A.: Pain in the left chest: some considerations in local practice, M. Press and Circ. **20**: 474, 1948.
14. Roberts, S. R.: Nervous and mental influences in angina pectoris, Am. Heart J. **7**: 21, 1931.
15. Burnett, C. T.: Pain and pain equivalent in heart disease, Ann. Int. Med. **10**: 1156, 1937.
16. Reeves, T. J., and Harrison, T. R.: Diagnostic and therapeutic value of the reproduction of chest pain, Arch. Int. Med. **91**: 8, 1953.

SERUM CONCENTRATIONS OF VITAMIN B_{12} IN ACUTE LEUKEMIA *

By Marion F. Beard, M.D., F.A.C.P., W. R. Pitney, M.D., M.R.A.C.P., Everett H. Sanneman, M.D., Marvin J. Sakol, M.D., and Harry H. Moorhead, M.D., *Louisville, Kentucky*

In a previous paper,[1] serum concentrations of vitamin B_{12} in patients suffering from chronic leukemia were reported. It was shown that, in chronic lymphocytic leukemia, serum contains a normal concentration of the vitamin, whereas in chronic myelocytic leukemia the concentration is markedly increased.

A preliminary report of serum vitamin B_{12} concentrations in seven cases of acute leukemia suggested that the variable concentrations found might be associated with morphologic differences in cell types such as occur in chronic leukemia. In this paper a morphologic diagnosis has been attempted in 20 cases of acute leukemia, and comparison made with the serum vitamin B_{12} concentration. The results indicate that the same pattern is followed in acute as in chronic leukemia. In cases of acute lymphocytic leukemia, serum concentrations of the vitamin are normal. In cases of acute myelocytic leukemia, markedly elevated concentrations are found.

Materials and Methods

Serum assays for vitamin B_{12} have been performed using *Euglena gracilis* as test organism. The method used was exactly that described by Ross.[2] This technic makes possible an estimate of the concentration of vitamin B_{12} existing as both free and bound in the serum. Because of the well known difficulties in classification of the cell type involved in many cases of acute leukemia, diagnosis in each case was made independently by five observers without knowledge of the result of serum vitamin B_{12} assay. Blood and bone marrow preparations were examined by the supravital technic, using the stains janus green and neutral red. Fixed films were stained by a combination of Jenner's and Giemsa's stains at pH 6.8. The usual criteria have been followed for the differentiation of cell types. As a check upon the accuracy of the opinions offered, all the fixed stained films have been reviewed prior to the writing of this paper.

Results

In table 1 the 20 cases of acute leukemia are grouped according to the morphologic diagnosis. There was surprising agreement among observers

* Received for publication March 10, 1954.
This study was made possible by a grant from the National Institutes of Health, Bethesda, Maryland, under grant number A-112.

TABLE I

Serum Vitamin B_{12} Concentrations in Acute Leukemia

Patient	Morphologic Diagnosis	Serum Vit. B_{12} Conc. ($\mu\mu$g./ml.)
G. A.	Lymphocytic*	340
D. McK.	Lymphocytic	252
D. P.	Lymphocytic	284
L. W.	Lymphocytic	376
D. T.	Lymphocytic	189
S. S.	Lymphocytic	216
A. H.	Lymphocytic	396
H. R.	Lymphocytic	184
R. S.	Lymphocytic	372
L. M.	Lymphocytic	228
R. O'B.	Lymphocytic	116
B. H.	Monocytic†	630
J. W.	Monocytic	768
J. I.	Monocytic	564
M. B.	Myelocytic	1,000
J. C.	Myelocytic	2,016
J. S.	Myelocytic	1,920
B. L.	Myelocytic*	1,460
D. C.	Myelocytic	9,200
J. M.	Myelocytic	1,100

* One observer considered the cell type to be monocytic.
† One observer considered the cell type to be lymphocytic, another to be reticulum cell.

in nearly all instances. In case G. A., one observer considered the cell type to be monocytic, while the remainder considered it lymphocytic. In case B. L., one observer considered the cell type to be monocytic, while the remainder considered it myelocytic. In case B. H., where the cell involved was primitive, classification was recorded as monocytic leukemia, reticulum cell leukemia and lymphosarcoma. The difficulty in assessing these primitive types of leukemia is well known. Eleven cases were considered acute lymphocytic, six acute myelocytic and three monocytic.

In table 1 the serum vitamin B_{12} concentrations are also recorded. In the 11 cases of acute lymphocytic leukemia the range of serum vitamin B_{12} concentration was from 116 to 396 $\mu\mu$g./ml., with a mean of 270 $\mu\mu$g./ml. In all instances the vitamin was assayed totally in the bound form. In 56 normal sera we have found the vitamin B_{12} concentration to vary from 86 to 460 $\mu\mu$g./ml., with a mean of 212 $\mu\mu$g./ml. In 52 of these sera the vitamin was assayed as totally bound. In the other four, small amounts of free vitamin were present. The mean of bound vitamin B_{12} concentration for the whole group was 207 $\mu\mu$g./ml. The cases of acute lymphocytic leukemia therefore show a normal serum vitamin B_{12} concentration.

The six cases of acute myelocytic leukemia showed a range of serum vitamin B_{12} concentration from 1,000 to 9,200 $\mu\mu$g./ml. The mean of 2,760 $\mu\mu$g./ml. is approximately 13 times the mean for normal sera. In five cases there were small amounts of free vitamin present. The mean concentration of bound vitamin was 2,570 $\mu\mu$g./ml.

The three cases of acute monocytic leukemia showed a moderate elevation

in serum vitamin B_{12} concentration, a range from 564 to 776 $\mu\mu$g./ml., with a mean of 650 $\mu\mu$g./ml. being recorded.

Correlation of Serum Vitamin B_{12} Concentration and White Cell Count

In figure 1 the serum vitamin B_{12} concentrations have been plotted logarithmically against the peripheral white cell count estimated at the same time. There are 25 observations on the 20 patients. It is seen that there is no correlation in any group between the total white cell count and the serum concentration. The lowest concentration recorded in the acute myelocytic group was 1,000 $\mu\mu$g./ml. This was obtained from patient M. B. while the white cell count was 38,000/cu. mm. The highest concentration recorded was 9,200 $\mu\mu$g./ml., in patient D. C. This patient was leukopenic throughout his illness, and the white cell count was 1,000/cu. mm. at the time blood was drawn for vitamin B_{12} assay.

In the acute lymphocytic group, white cell counts ranged from 1,000 to 73,000/cu. mm. All cases, however, showed a normal serum concentration of vitamin B_{12}.

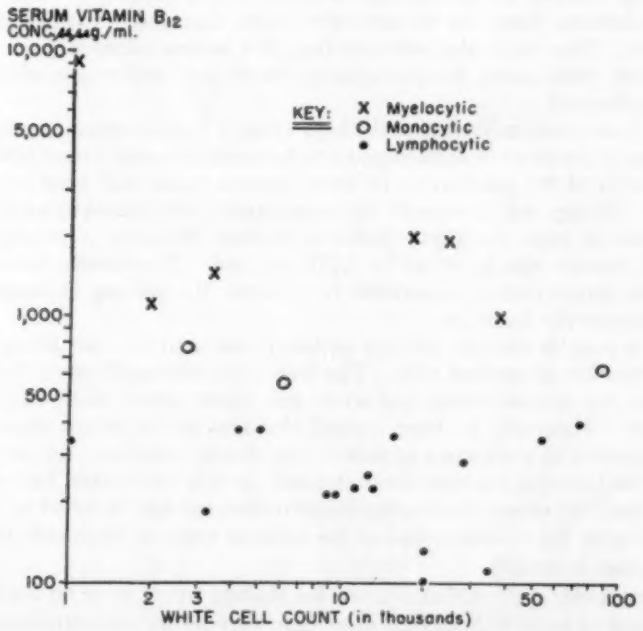


Fig. 1. Serum vitamin B_{12} concentrations and white cell counts in acute leukemia.

Effects of Treatment on the Serum Vitamin B_{12} Concentration

These patients were treated with the therapeutic measures at present available. Blood transfusions were given to combat anemia. When indicated, cortisone, ACTH, A-methopterin, 6 mercaptopurine and nitrogen mustard were used. None of the cases of acute myelocytic leukemia experienced a remission, and so it is not possible to say if the abnormally high serum vitamin B_{12} concentrations fall during remission. In chronic myelocytic leukemia, concentrations do fall when the white cell count is reduced by either x-ray or urethane therapy,[1] but remain above normal even when a normal white cell count is achieved. Remission was achieved in five of the cases of acute lymphocytic leukemia. Serum vitamin B_{12} concentrations were normal in these cases at the commencement of therapy, and remained normal in those in which multiple observations were made.

Discussion

There is evidence that various therapeutic agents vary in their effects on different cell types in acute leukemia. For this reason it is desirable to attempt classification of such cases according to cell type. The differences in serum vitamin B_{12} concentrations noted in this paper give confirmation to conclusions, based on morphologic study, that such classifications are possible. This study also indicates that, if a serious effort is made to differentiate these cases morphologically, surprising uniformity of opinion can be obtained.

It seems most unlikely that the high vitamin B_{12} concentrations found in the sera of the cases of acute myelocytic leukemia play any causal rôle in the production of the condition. In vitro, normal serum will bind only from 208 to 576 $\mu\mu$g./ml. of vitamin B_{12} when excess free vitamin is added.[3] In the cases of acute myelocytic leukemia studied, the mean concentration of bound vitamin was found to be 2,570 $\mu\mu$g./ml. The results demonstrate that the serum protein responsible for vitamin B_{12} binding is abnormal in acute myelocytic leukemia.

It is possible that the binding protein is liberated into the serum by the disintegration of myeloid cells. The lack of correlation between the serum vitamin B_{12} concentrations and white cell counts would make this appear unlikely. However, we have noticed elevation in the serum vitamin B_{12} concentration in some cases of leukocytosis due to infection. In such cases, when the infection has been controlled and the white cell count has returned to normal, the serum vitamin B_{12} concentration has also reverted to normal. The vitamin B_{12} concentrations of the different types of white cells have not as yet been reported.

Our results suggest that vitamin B_{12} therapy would be of no avail in the treatment of acute leukemia, as in no case were serum concentrations found below normal. This is confirmed by clinical experience.[4]

Summary

Serum vitamin B_{12} concentrations have been determined in 20 cases of acute leukemia. Eleven cases of acute lymphocytic leukemia showed a normal serum concentration. Six cases of acute myelocytic leukemia showed greatly elevated serum concentrations of the vitamin. In three cases of acute monocytic leukemia, moderate elevations were noted.

The desirability of morphologic differentiation of cell type involved in acute leukemia has been pointed out.

BIBLIOGRAPHY

1. Beard, M. F., Pitney, W. R., and Sanneman, E. H.: Serum concentrations of vitamin B_{12} in patients suffering from leukemia, Blood, in press.
2. Ross, G. I. M.: Vitamin B_{12} assay in body fluids using *Euglena gracilis*, J. Clin. Path. **5**: 250, 1952.
3. Pitney, W. R., Beard, M. F., and VanLoon, E. J.: Observations on the bound form of vitamin B_{12} in human serum, J. Biol. Chem., in press.
4. Welsh, I.: Failure of massive doses of vitamin B_{12} in acute leukemia, Brit. M. J. **2**: 1133, 1952.

MODERN MANAGEMENT OF PULMONARY TUBERCULOSIS: PRINCIPLES AND CONCEPTS*

By R. A. Goodwin, Jr., M.D., F.A.C.P., *Nashville, Tennessee*

For nearly half-a-century tuberculosis became increasingly isolated from the field of internal medicine as the sanatorium movement developed. The recent era of anti-tuberculosis drugs and surgical resection has re-stimulated the interest of the internist in this important disease. Certain principles and concepts governing the current management of pulmonary tuberculosis are presented.

The final outcome in treated pulmonary tuberculosis is dependent upon the influence of therapeutic measures on the fundamental host-parasite relationship. Effective use of therapy must take into account concepts of pathogenesis of the disease and some knowledge of the basic mechanisms of healing. The basic principles of pathogenesis may be seen in the behavior or potential behavior of the individual patch of tuberculous bronchopneumonia. Where the inflammatory reaction is of sufficient intensity there is a marked tendency for tissue necrosis to take place. Because of circumstances not at present understood, this necrotic tissue tends to resist autolysis and characteristically persists in a semi-solid state termed caseous-necrosis.

In the economy of the host the closed necrotic area plays a somewhat paradoxic rôle. A physical and chemical environment bacteriostatic for the tubercle bacillus results from the lowered oxygen tension, the presence of certain organic acids and other circumstances unfavorable to the growth of the infecting organisms. Large numbers of tubercle bacilli die off in closed necrotic tissue. However, a few remain and may persist in a potentially viable state for many years. When circumstances become unfavorable for growth, the tubercle bacillus frequently has the capacity to retreat into a dormant, resting phase in which it may exist in the host tissues for long periods of time, only to return to a growing phase should conditions become favorable. These characteristics of the organisms, and the host-response that provides persistent necrotic tissue to harbor them, furnish the factors which establish the chronicity of tuberculosis, and account for most of the problems in therapy.

The necrotic focus at any time, early or late, may be subject to little understood chemical changes which result in autolysis and liquefaction. The lesion sloughs and empties into a bronchus. Tubercle bacilli grow rapidly

* Presented at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 9, 1954.

From the Tuberculosis Service, Veterans Administration Hospital, and the Department of Medicine, School of Medicine, Vanderbilt University, Nashville, Tennessee.

in the sloughing tissue and necrotic cavity walls, and are disseminated to other parts of the lung through the bronchial communications.

The fact that relatively few who are infected with the tubercle bacillus ever develop significant clinical disease is evidence that native resistance and acquired immunity are usually highly effective. On the other hand, once progressive disease has become established the mechanisms of immunity and resistance appear slow, uncertain and indecisive, and lack vigor compared to host responses in most of the acute infections. In spite of many years of investigative endeavor, the precise mechanisms of host resistance and immunity are essentially unknown. Immune factors, native and acquired, do not appear to be humoral but rather reside within the cells and tissues.

The anatomic mechanisms of healing are fairly clear cut, and are qualitatively the same regardless of the influence of natural or therapeutic factors. Non-necrotic exudate, if circumstances are favorable for the host, may in large part resolve, leaving undamaged normal tissue. Unresolved, non-necrotic components heal by replacement with fibrous tissue. The necrotic residual, however, may heal only by slow fibrous encapsulation. Slow inspissation and infiltration with calcium salts (as with any type of persistent necrotic tissue) may occur over a period of years. The necrotic residual characteristically harbors for years a few metabolically dormant but potentially viable tubercle bacilli which may at any time cause relapse of disease. For some of the smaller necrotic foci, healing may be curative. In general, the larger the necrotic residual the more insecure is the healing and the greater the tendency toward relapse.

The circumstances of cavity closure are important from the standpoint of prognosis and therapeutic considerations. The cavity may slough out cleanly and close, approximating walls of granulation tissue which can heal securely as a clean, non-necrotic scar. When the cavity closes before sloughing out cleanly, it sandwiches in the necrotic walls. If drainage is obstructed and the cavity fills with retained secretions, the unstable "blocked cavity" or filled-in cavity results. In either case, potentially dangerous chronic infection persists.

Modern management of pulmonary tuberculosis demands the most effective use of chemotherapy, rest treatment and, when indicated, collapse measures and surgical resection. The general goal of treatment is the attainment of maximal resolution of reversible disease, the closure or eradication of open lesions, and the most secure healing possible of chronic residuals. Because of the persistence of necrotic residuals which harbor living tubercle bacilli, no method of treatment yet available can be expected in itself, directly, to cure tuberculous infection. A lasting arrest of the disease is dependent upon healing mechanisms of host resistance.

The time-honored use of rest therapy in pulmonary tuberculosis has been established almost entirely on an empiric basis. Rest treatment implies a

program designed to attain maximal physical rest and mental and emotional relaxation during the acute phases of healing, and then increasing activity and general rehabilitation. Decrease in the mechanical motion of the diseased lung, decrease in volume (collapse) of the lung as a result of the horizontal position, and the elimination of fatigue explain in part—but far from completely—the beneficial effect of rest in bed. Although there remains some disagreement as to the necessary strictness of bed-rest, rest therapy has been accepted as the basic method of treatment in pulmonary tuberculosis.

For many years collapse procedures have enjoyed a prominent position in the management of tuberculosis and have proved helpful in reversing progressive disease and in effecting cavity closure. The rationale of collapse therapy is that decrease in the volume of the lung favors cavity closure and healing through lessened elastic tension in the diseased area and decrease in mechanical motion. In current practice, the use of pneumothorax has almost disappeared. Separation of the pleural surfaces in the face of acute disease led to a high incidence of empyema, bronchopleural fistula, unexpandable lung and loss of pulmonary function due to thickened pleura. The use of pneumoperitoneum, with its low incidence of complications, has carried over into the chemotherapy era. Although not universally practiced, this reversible procedure is considered useful in some cases as an aid to cavity closure, particularly in the presence of bilateral disease and lower lung field cavities persisting after adequate trial on rest and chemotherapy. Thoracoplasty has stood the test of time as a valuable method of cavity closure and control of destroyed lung tissue when the disease is situated in the upper posterior portions of the lung fields.

Antimicrobial therapy in tuberculosis has had a profound effect upon the potential for control of the disease in the individual case. More effective control over bacterial growth accelerates the reversal of progressive disease and the institution of mechanisms of healing. Resorption of non-necrotic exudate is strikingly enhanced. The combination of prolonged chemotherapy and rest therapy is potentially curative in healing non-necrotic disease, but falls short of complete eradication of infecting organisms in necrotic tissues.

As a result of the greatest coöperative medical study in history, many facts have become established in regard to the clinical effect of more than a score of antituberculosis drugs and many combinations. The combination of streptomycin and para-aminosalicylic acid (PAS) has emerged as the most effective proved antimicrobial agent. The effect of the combination in preventing streptomycin resistance permitted the use of long-term drug suppression, and the principle of prolonged chemotherapy, a logical aim in the control of tuberculosis, became established. Although the proper duration of drug treatment has not been clearly defined in various types of disease, it is general practice to continue combined therapy until the disease can be classified as "inactive" or, in other words, until six months after

cavity closure, sputum negativity and roentgenogram stability have been attained.

Isoniazid, a second potent antituberculosis drug, is still receiving extensive clinical trials. In general, it appears that isoniazid alone is the therapeutic equivalent of streptomycin and PAS for the first few months. Isoniazid has two theoretic advantages: it penetrates more readily into necrotic tuberculosis tissue, and it is effective against intracellular organisms, which is not the case with streptomycin. Whether these are practical advantages in long-term treatment of tuberculosis has not been determined. The eventual rôle of isoniazid in prolonged chemotherapy and its most effective use in combination with other drugs have yet to be defined.

Under the tuberculostatic influence of chemotherapy, surgical resection of pulmonary tissue in tuberculosis became possible at a reasonable cost in terms of operative mortality and complications. Since rest and chemotherapy fell short of complete control of certain types of necrotic lesions, it was a logical aim to attempt to remove these surgically. This principle has been applied successfully to two major problems: the removal of otherwise uncontrollable cavitary or necrotic tissue in order to make arrest of the disease possible, and the removal of potentially dangerous necrotic residuals in order to minimize the chance of relapse in the future.

It is important to develop a plan of therapy for each case, individualized as far as possible by an evaluation of the character of the disease and the potential effectiveness of host immunity, and then modified as necessary according to later developments. A vigorous, uninterrupted program of treatment, instituted as early in the course of the disease as possible, undoubtedly offers the best results. In such a plan, bed-rest and prolonged chemotherapy constitute the basic treatment régime and can be expected to be curative in time against most non-necrotic tuberculous infection. Small necrotic remnants may be permanently healed. Large necrotic residuals and filled-in cavities constitute a threat of relapse and, if it is feasible, such lesions may be surgically resected at the appropriate time during the course of prolonged antimicrobial therapy. Many cavitary lesions may permanently close under chemotherapy and rest. If after a trial this does not seem likely, a temporary collapse measure may be helpful. After the fifth or sixth month of persistent cavitation, the incidence of development of drug resistance mounts. This is then the period of election for surgery, unless it is contraindicated. Thoracoplasty is frequently used for upper, posteriorly situated lesions, and resection for these and for lesions elsewhere. Rest and chemotherapy are continued through and after the surgical period, depending upon the character of the residual disease. Even if all gross lesions are surgically resected, small remnants invariably remain and must be adequately treated and healed. Following the active treatment period and a gradual increase in activity, there is a program of rehabilitation and the patient is prepared for a way of life as normal as is consistent with his disability and hazard of relapse of disease.

Not many years ago the primary goal in the treatment of tuberculosis was to save life. Under modern management this is expected in most circumstances, and the goal of treatment has extended past arrest of the disease and emphasizes prevention of relapse in the future. According to conservative present-day philosophy, treatment should be vigorous, uninterrupted and complete, with secure healing rather than the "saving of time" as the guiding principle.

An interesting bacteriologic development in relation to isoniazid demonstrates the complexity of the host-parasite relationship in tuberculosis. It was demonstrated that tubercle bacilli which developed resistance to isoniazid in vitro or in vivo lost their virulence for guinea pigs. This aroused speculation that isoniazid would either kill the tubercle bacillus or render it avirulent. It is now clearly established that isoniazid-resistant, guinea pig-avirulent organisms are capable of causing spread of disease in the human host. Also, the guinea pig-avirulent strains produce typical disease in the mouse.

Pathologic and bacteriologic study of resected lesions from patients who had received prolonged drug treatment showed that in many cases, even though organisms could be demonstrated on smear and in histologic preparations, the tubercle bacilli would not grow in artificial media or produce disease in animals by usual laboratory technics. This has raised the question as to whether prolonged chemotherapy has rendered the organisms nonviable. Some have accepted this implication, that drug treatment has indeed effectively sterilized even the necrotic lesions, and therefore consider prolonged chemotherapy as essentially "definitive" treatment. This concept, if true, would invalidate the principle of surgical removal of the filled-in cavity or the large necrotic focus. This concept has also led to the speculation as to whether prolonged rest therapy is necessary. Conservative thought points out that the necrotic lesion itself has the property of altering the capacity of the tubercle bacillus to grow under usual laboratory conditions, and yet this type of lesion is characteristically associated with relapse of disease. It is suggested that usual laboratory methods may not readily allow for a return to active growth habits of the metabolically dormant organism. There is also no evidence that the present antimicrobial drugs continue to exert an influence once the organism has retreated into a quiescent metabolic phase. These and other questions relating to the permanency of prolonged drug treatment must await a careful study of relapse tendencies.

CASE REPORTS

ENDOCARDIAL FIBRO-ELASTOSIS WITH MARKED CARDIAC ENLARGEMENT AND FAILURE IN A MAN WHO DIED AT THE AGE OF 71 AFTER 15 YEARS OF ANGINA PECTORIS AND TWO YEARS OF CONGESTIVE HEART FAILURE *

By Paul D. White, M.D., F.A.C.P., and Robert H. Fennell, Jr., M.D.,
Boston, Massachusetts

Endomyocardial fibro-elastosis has become recognized as an important cardiovascular disease.[1, 2, 3, 4, 5, 6] Its cause is still obscure but it has been found at autopsy in a good many individuals throughout the world. Most of these cases on record are infants, children or young adults. The presence of this condition in an old man followed clinically for many years, constitutes at present almost a unique variation of this condition, and justifies this report.

Case Report

Mr. D. C. H. came to consult one of us (P. D. W.) in August, 1923, at the age of 41 years. He was a business man, secretary of a mill, and was at that time unmarried. He gave a story of having years before "strained his heart" while rowing at college in 1906, but he recovered quickly from that and there was no evidence of anything wrong with his heart at the time of the examination in 1923. He had passed life insurance easily within a year but while undergoing a routine annual examination in May, 1922, was told that his heart needed attention. He had no symptoms. Physical examination showed no abnormalities. His heart was normal in size, sounds, rate and rhythm. There was no evidence of congestive failure. The blood pressure measured 110 mm. mercury systolic and 70 mm. diastolic. His electrocardiogram was perfectly normal at a rate of 75. The diagnosis of normal heart plus apprehension was made and he was completely reassured.

Seven years later, on June 13, 1930, he brought his mother for examination and said that he himself at that time felt perfectly well. He looked healthy but was not himself examined on that occasion.

On May 20, 1938, 15 years after his earlier examination, he again asked for advice, stating that he had been perfectly well during the previous years until recently when, while dancing, he had had slight substernal oppression which recurred a fortnight later when lifting some books. He was active physically, working hard in his garden. He used no tobacco or alcohol, and had changed very little in weight. He had married nine years earlier, in 1929. Physical examination showed no abnormalities. His pulse was regular at a rate of 60. The blood pressure was 140 mm. systolic and 90 mm. diastolic. There was no evidence of congestive failure. Fluoroscopy showed an apparently normal though full-sized heart, with clear lungs.

* Received for publication November 28, 1953.
Comments on this case were made at the Clinicopathological Conference at the Massachusetts General Hospital on August 13, 1953, and were published in the New England J. Med. 249: 734 (Oct. 29) 1953.

By orthodiagram the transverse diameter of the heart measured 12.0 cm. and the internal diameter of the thorax 25.2 cm. The electrocardiogram showed ventricular premature beats at a rate of 70, with slight to moderate left axis deviation and upright T waves in all four leads. A diagnosis of probable coronary insufficiency was made and he was advised to avoid exercise that would bring on discomfort and to lose five pounds in weight.

Four months later he came for examination again and complained of the same symptom, of slight substernal oppression on walking upgrade in cool air. Again nothing wrong was found on examination except that the heart seemed to be a little larger by orthodiagram; the transverse diameter measured 12.4 cm. The T waves in Lead I were somewhat lower. Again it was thought that coronary insufficiency was present.

The next examination was on June 19, 1939, when he reported himself as being quite well, with no angina pectoris at all. He had lost 12 pounds by diet. Physical examination was perfectly normal and both x-ray examination and electrocardiogram seemed at that time normal. The transverse diameter of the heart by orthodiagram on this occasion measured 11.9 cm. It was thought that he had done very well indeed. A review of the electrocardiogram later suggested transient bundle branch block in the last few beats of Lead IV.

In December, 1940, he came for another examination and reported good health except for the occurrence of infectious mononucleosis in the summer of 1939 and a recurrence of substernal oppression on effort on three occasions during the previous three months. Physical examination showed no abnormalities except for occasional bigeminy due to premature beats. Fluoroscopy showed normal findings. The electrocardiogram revealed many ventricular premature beats at a heart rate of 70 to 80, with rather wide QRS waves. A comment was made that there was a slight recurrence of angina pectoris.

In June, 1941, he reported excellent health during the previous six months except on a few occasions, when he had moderate substernal oppression while walking quickly or in hilly country. Physical examination showed no abnormalities except for an intermittent pulse due to premature beats at a heart rate of 78. The blood pressure was 150 to 160 mm. systolic and 90 mm. diastolic in both arms. There was a slight to moderate systolic murmur at the apex of grade 2 to 3. Fluoroscopy showed a full-sized heart with clear lung fields. By orthodiagram the transverse diameter of the heart measured 12.1 cm. and the internal diameter of the thorax 25.4 cm. The electrocardiogram showed ventricular premature beats at a heart rate of 80, with variable paroxysmal left bundle branch block, diphasic T waves in Lead I, and small R waves in Lead IV. The conclusion was that there was some evolution of coronary heart disease, as indicated by symptoms and by the bundle branch block, but that his condition was fairly good.

In December of that same year, 1941, he spoke of an increase in angina pectoris during the previous fortnight. He was now 59 years old. There was no change on physical examination. The electrocardiogram showed frequent ventricular premature beats at a heart rate of 80, with left bundle branch block except after compensatory pauses, when the QRS waves were of normal width. The T waves in Lead I were inverted. The note then was that there was a much limited coronary reserve, with a question of impending acute occlusion. He was advised to rest for a few weeks, though not in bed, and to try aminophylline. Following that he improved a good deal but his electrocardiogram continued to show the left bundle branch block.

In April, 1942, he stated that he had had during the previous few months a number of attacks of characteristic angina pectoris while exerting himself a little more than usual, and on one occasion he had felt faint. There had been much emotional strain because of his mother's acute illness and death. Physical examina-

tion showed no change. Fluoroscopy, however, revealed a larger heart by orthodiagram; the transverse diameter had increased to 12.8 cm. The electrocardiogram was unchanged and showed occasional ventricular premature beats at a rate of 85, with left bundle branch block.

Because of the increase in trouble he was seen after a shorter interval on the next occasion, in August, 1942. He reported that he had been well except for four brief attacks of substernal oppression on unusual effort. He was resting and doing very little work. Physical examination showed no important change. He had gained a little weight, up to 164 pounds dressed without his coat. The blood pressure was 140 mm. systolic and 90 mm. diastolic. His pulse rate was 72, with occasional premature beats. The heart showed mediocre sounds, with a slight systolic murmur heard over the precordium. Fluoroscopy showed a still larger heart, the transverse diameter measuring 13.2 cm. The lungs were clear. The electrocardiogram showed no change.

Examination in December, 1942, revealed no changes either in symptoms (occasional angina pectoris), physical examination, fluoroscopy or electrocardiogram.

In June, 1943, he reported improved health. He had spent several months in Florida and had had only rare attacks of substernal oppression on walking after meals. Physical examination showed a reduction in weight to 158 pounds without his coat. The pulse was intermittent at a rate of about 60. The blood pressure was 130 mm. systolic and 80 mm. diastolic. There was no evidence of congestive failure. The heart showed very mediocre sounds, with a grade 2 to 3 apical systolic murmur heard rather widely. Fluoroscopy showed an increasingly larger heart, the transverse diameter by orthodiagram measuring 13.7 cm.; the shape was globular. The lungs were clear. The electrocardiogram was unchanged, showing frequent ventricular premature beats, left bundle branch block and inverted T waves.

In December, 1943, he seemed symptomatically somewhat improved; he was still bothered, however, by some substernal oppression on effort after meals when the wind was in the north. He was about to go to Florida. Physical examination showed no change. The heart sounds were still mediocre. The pulse was intermittent at a rate of 60. The blood pressure was 150 mm. systolic and 80 mm. diastolic. There was no edema. There was still a grade 3 precordial systolic murmur heard both at apex and base. Fluoroscopy showed a moderately enlarged, globular heart. By orthodiagram the transverse diameter measured 14.3 cm. The lungs were clear. He was continued on nitrite and aminophylline as required.

In June, 1944, he reported considerable improvement, having substernal oppression on effort only very infrequently, when hurried. He was able to do a moderate amount of gardening without difficulty. Physical examination showed a good weight loss of five pounds and an intermittent pulse due to trigeminy, every third beat being premature at a heart rate of 72. The blood pressure was 145 mm. systolic and 90 mm. diastolic. The heart sounds were mediocre, with slight apical and left sternal border systolic murmurs. There was no evidence of congestive failure. Electrocardiogram showed trigeminy due to ventricular premature beats at a heart rate of 75, complicated by left bundle branch block. Fluoroscopy showed a moderately enlarged, globular heart, a little smaller than at the previous examination. The lungs were clear. He was advised to carry on sensibly, avoiding hurry, worry, overexertion, overeating and severe weather.

In November, 1944, he stated that he had been in fairly good health all summer and fall, with very rare angina pectoris on walking briskly after breakfast. He had used nitroglycerin only once. Physical examination showed no significant change. Electrocardiogram revealed left bundle branch block as before, with a little more inversion of the T waves in Lead I and frequent ventricular premature beats.

Fluoroscopy showed a smaller heart, distinctly better, with a transverse diameter of only 13.3 cm. The lungs were clear.

In June, 1945, he came again to the office reporting a good winter and considerable activity. For the first time in months he had had, two days earlier, a little substernal oppression on excitement, but this was cleared quickly by nitroglycerin. This was followed by two more spells the day before the visit to the office. Physical examination showed the pulse rate occasionally premature at 76. The blood pressure was 145 mm. systolic and 90 mm. diastolic. The heart sounds were mediocre, with a slight precordial systolic murmur. The heart size seemed a little larger again. The cardiac apex was very rounded. The lungs were clear. By orthodiagram the transverse diameter of the heart measured 13.8 cm. The comment was "recurrent coronary insufficiency, possibly due to a small fresh coronary thrombosis." He was advised to rest for a fortnight or so, to use nitroglycerin as required, and to take some aminophylline.

He was seen again in September, 1945, after a good summer in Maine, bothered only on occasion by substernal oppression on effort or excitement after meals, about 15 times altogether, quickly relieved by nitroglycerin, which he had used 19 times in 81 days. Physical examination showed a somewhat louder systolic murmur of grade 3. The electrocardiogram showed frequent ventricular premature beats, at times every second or third beat, at a heart rate of 75, with left bundle branch block and inverted T waves in Lead I.

In June, 1946, his report was favorable except for "grippe" in Florida in February and substernal oppression on effort after meals, quickly relieved by nitroglycerin. There was no change on examination or by electrocardiogram. Fluoroscopy showed a somewhat larger heart. The lungs were clear. By orthodiagram the transverse diameter of the heart measured 14.1 cm.

In November, 1946, he reported frequent recurrence of mild substernal oppression following his brother-in-law's sudden death a few weeks earlier. He was taking nitroglycerin once to three times a day. There was no change on physical examination, electrocardiogram or fluoroscopy.

On June 20, 1947, he was examined again and still complained of substernal oppression if he hurried, nitroglycerin always quickly relieving him. He was now 65 years old. His weight was satisfactory. His pulse was occasionally irregular at 72. The blood pressure was 140 mm. systolic and 90 mm. diastolic. The heart showed poor sounds, with a grade 3 systolic murmur best heard at the lower end of the sternum. Electrocardiogram showed frequent atrial premature beats at a rate of 75, with left bundle branch block and inverted T waves in Lead I. Fluoroscopy showed a larger heart with a normal sized aorta. The lungs were clear. By orthodiagram the transverse diameter of the heart measured 14.6 cm., which was nearly 1.5 cm. larger than the measurement in November, 1944.

On July 3, 1948, he was complaining as much as before of angina pectoris about once a day when under nervous strain or overactive. He had begun to take digitalis following some shortness of breath that had come on during the winter while he was in Florida. However, he was not taking this medicine regularly. There was no change on physical examination, electrocardiography or fluoroscopy. He was advised to take digitoxin, 0.10 mg. daily.

On June 20, 1949, he was examined again in the office and reported having had daily attacks of angina pectoris which he was treating and preventing effectively by nitroglycerin; he was using that medicine several times a day. He thought that the angina pectoris was more easily induced than in the past, but he complained of no dyspnea. Physical examination showed him apparently in good health, with a regular pulse of 72. The blood pressure was 145 mm. systolic and 95 mm. diastolic. There was no edema. The heart showed mediocre sounds, with a grade 2 precordial

systolic murmur. The electrocardiogram showed normal rhythm, with ventricular premature beats at a rate of 80, left bundle branch block as before, with inverted T waves in Leads I and V_6. Fluoroscopy showed an enlarged, round heart shadow, much as before, with clear lungs. By orthodiagram the transverse diameter of the heart measured 14.2 cm. He was continued on nitroglycerin as needed, and Purodigin (digitoxin) 0.1 mg. daily.

On October 20, 1949, he seemed a little better. He was now 68 years old. There was no change on physical examination, electrocardiography or fluoroscopy.

On May 11, 1950, while in Florida, he was awakened in the night by orthopnea but recovered quickly; and in June, when he was examined in Boston, he was found to be in fairly good health, though with a good deal of angina pectoris on effort. Physical examination showed a pulse rate of 60, a blood pressure of 140 mm. systolic and 90 mm. diastolic, a very slight trace of edema over both shins, an enlarged heart with poor sounds, and a question of an apical diastolic gallop rhythm. The neck veins were not engorged. The electrocardiogram showed left bundle branch block at a heart rate of 80, with a few premature beats and inverted T waves in Lead I. Fluoroscopy showed a larger heart than before, with clear lung fields. By orthodiagram the transverse diameter of the heart measured 14.8 cm. He was advised to use care to avoid strains, to take digitalis daily and nitroglycerin freely, and to reduce his sodium intake.

In October of that year, 1950, he continued to complain of much angina pectoris, which occurred about three times a day. He did not look so well. His pulse was regular at a rate of 80. The blood pressure was 140 mm. systolic and 85 mm. diastolic. The heart sounds were poor, with a widely heard grade 3 systolic murmur, loudest at the lower end of the sternum. The electrocardiogram showed ventricular premature beats at a rate of 110, with left bundle branch block. Fluoroscopy showed moderate enlargement of the heart, much as before, with clear lungs.

In May, 1951, in Florida, he again had attacks of nocturnal dyspnea for several successive nights and was given, in addition to his regular treatment, mercurial diuretics. When he arrived back in Boston a month later he had improved a good deal. He had much less angina pectoris and little or no dyspnea. Physical examination showed loss of weight. The pulse rate was 84, with rare extrasystoles. There was no edema. The heart showed mediocre sounds, with slight gallop rhythm at the apex, a grade 3 apical systolic murmur, and a grade 2 aortic systolic murmur. The electrocardiogram showed rare ventricular premature beats at a heart rate of 90, with left bundle branch block and inverted T waves in Lead I. Fluoroscopy showed a much bigger heart, with clear lungs. By orthodiagram the transverse diameter of the heart measured 15.8 cm.

In October, 1951, he reported having had a fairly good summer and fall in Maine, with little dyspnea but frequent substernal oppression, relieved or prevented by nitroglycerin. He was taking digitoxin, 0.15 mg. daily, and was careful about his salt intake. Physical examination showed some improvement, with absence of gallop rhythm and a less loud murmur, now grade 2 systolic, at the apex. The electrocardiogram showed normal rhythm at a rate of 70, with at times sinus bradycardia and ventricular escape, along with left bundle branch block. Fluoroscopy showed a somewhat smaller but still large heart. By orthodiagram the transverse diameter measured 14.9 cm. The lungs were clear. The comment was that he was still on the ragged edge of coronary and myocardial insufficiency, with guarded prognosis.

In May, 1952, a report from Florida was of a satisfactory condition, despite the strain of his wife's serious illness with carcinoma. Because of his wife's illness and his own health he remained in Florida throughout the rest of the year.

On January 13, 1953, under the strain of his wife's illness, he lapsed into a

precarious state of health, on the edge of left ventricular failure much of the time.

On May 1, 1953, a report from Florida (kindness of Dr. Williams, of Daytona Beach) was that because of his impending failure in January he was given mercurials. However, he was admitted to the local hospital in April because of recurrent nocturnal dyspnea. This had followed his wife's death in February. Oxygen and complete bed-rest with digitalis, mercurials and ammonium chloride were prescribed. He slowly improved.

He returned north in early May, 1953, and arrived somewhat improved. For the first time then he showed atrial fibrillation at a heart rate of 64.

Our last examination of him was on June 1, 1953, in the office. He had had a most miserable year, as outlined in the notes above. His chief complaints were much abdominal discomfort, with gas, chilliness and bone-ache after mercurial injections, weakness, dyspnea, anorexia and some stomatitis. Physical examination showed him thin, sallow and cyanotic. His weight was 136½ pounds, 11 less than in 1951. The pulse was irregular at 100 +. The blood pressure was 95 mm. systolic and 65 mm. diastolic. There was a slight deep systolic jugular pulse. There was no edema of the shins. The heart showed poor sounds, with a grade 2 to 3 systolic murmur, heard best along the lower border of the sternum. The liver was enlarged and tender and there was considerable intestinal gas. The lungs were clear. An electrocardiogram showed atrial fibrillation, rate 100, with left bundle branch block. Fluoroscopy showed a large heart, giving now the largest measurements recorded in this patient, with a transverse diameter of 16.8 cm. The lungs were clear.

Shortly after this, on June 6, 1953, he entered the hospital and died three hours after admission.

Postmortem examination was made and it was recorded as follows:

The body was that of a well developed elderly male 170 cm. long and weighing an estimated 160 pounds. There was mild edema of the ankles. The peritoneal cavity and left pleural space each contained 500 c.c. of clear fluid. The lungs were quite heavy, weighing 1,510 gm., and were extremely congested. Fluid exuded from the cut surfaces. The left lower lobe was compressed by the large left ventricle and was partially collapsed.

The heart was tremendous and weighed 890 gm. Both ventricles were dilated and hypertrophied; the wall of the left was 20 mm. thick and that of the right 4 mm. The myocardium was uniformly reddish brown and slightly paler than normal. The endocardium was thickened in patchy, irregular areas, especially along the outflow tracts of the ventricles. The valves were all normal except for dilatation of the rings of the mitral and tricuspid valves. The coronary arteries were widely patent. In the circumflex and anterior descending branches of the left coronary artery were several atheromatous plaques, but these did not significantly encroach upon the lumens.

The liver was slightly enlarged and congested. The spleen was of normal size but contained in its upper pole a 1 cm. by 3 cm. red-yellow focus and it, on section, involved a triangular area of the parenchyma. There were several cirsoid aneurysms in the splenic artery. The kidney surfaces were slightly granular but of normal size and appearance otherwise. The prostate was enlarged. The other organs were not remarkable. The aorta and its major branches were mildly atherosclerotic.

The left posterior tibial vein and the deep calf veins in the left leg contained reddish black, slightly granular thrombi which were loosely adherent at a few points.

The brain weighed 1,360 gm.; no old or recent infarcts or other abnormalities were found therein.

Microscopic: The endocardium was thickened, primarily by elastic tissue, but thin collagen fibrils were intermingled. The thickness varied considerably; in some areas it measured up to 450 micra, but was thinner in most of the sections, usually

FIG. 1. Microscopic section (× 400) of myocardium and grossly thickened endocardium from the left ventricle.

100 to 150 micra. The thickened endocardium was demarcated from the underlying muscle by a heavier elastic membrane, and beneath that were a few collagen fibers (figure 1). In occasional foci the endocardium seemed normally thin (30 micra). The myocardial fibers were large, the nuclei had square ends, and some were bizarrely

shaped. Except for the evidence of hypertrophy the myocardium for the most part was normal. There were scattered small foci of interstitial fibrosis, and a few muscle fibers were evidently replaced by scar tissue. The intima of the coronary arteries was thickened by fibrous tissue.

The pulmonary vessels were distended with blood and many alveoli contained pink edema fluid. In the spleen there was a small infarct. There was central necrosis surrounded by dilated vessels and proliferating fibroblasts. In the center of the liver lobules the sinusoids were dilated and liver cells had disappeared. The kidneys were normal except for hyalinization of a few glomeruli. A section of calf veins showed them filled with laminated thrombus with beginning organization.

Summary

We have recorded herewith an apparently unique case of endocardial fibroelastosis in a man who died of congestive heart failure at the age of 71 years, after 15 years of typical angina pectoris. He had apparently been in perfect health at the time of examination by one of us 30 years before his death. His course was characterized also by slowly enlarging heart size and the development of bundle branch block in the electrocardiogram. There was no obvious cause for the disease.

Addendum

Since the preparation of this paper we have encountered a somewhat similar case within a relatively few weeks. The history and autopsy findings are as follows:

History: B. M., a 53 year old man who worked part-time as a dishwasher, was admitted to the hospital July 13, 1953, with the chief complaint of shortness of breath.

Six years earlier the patient had first experienced exertional dyspnea, and pain in the epigastrium and left shoulder on effort that promptly disappeared with rest. These symptoms had persisted for approximately a year, when he was hospitalized elsewhere. He was told that the electrocardiogram showed "extra beats," and that he must avoid exertion and eat food without salt. The only medication given was digitalis. In the following several years he had similar symptoms and similar treatment. Dyspnea and orthopnea became more marked one year before admission and the pain was brought on by less exertion, was more severe and was substernal as well as epigastric and in the left shoulder. He occasionally was awakened at night by cramps in the right calf.

The past history was noncontributory. He had had no serious illnesses. He had, except for recent months, drunk 10 to 15 glasses of beer daily for many years.

Physical examination revealed a hyperactive, florid man of medium build who was lying at a 10° angle in bed, coughing occasionally but not in pain. The neck veins were flat when the patient sat up, and the thyroid gland was questionably palpable. There was no thyroid bruit. The lung fields were clear except for diminished breath sounds at the right base posteriorly. The heart was enlarged, with the left border 14 cm. from the midsternal line and the apex impulse at the sixth intercostal space. There was a high-pitched harsh apical systolic murmur, but no diastolic murmur. The aortic second sound was greater than the pulmonic. The rhythm was totally irregular without deficit. The abdomen was normal. There

was no peripheral edema. Arterial pulsations were palpable in all extremities. There was a slight fine tremor of the extended hands.

The temperature was 99° F.; pulse rate, 104; respirations, 20 per minute. The blood pressure was 154 mm. mercury systolic and 100 mm. diastolic.

The blood and urine were within normal limits.

An electrocardiogram showed atrial fibrillation and left bundle branch block.

A chest roentgenogram showed the cardiothoracic ratio to be 18.5 to 31.5, with left ventricular enlargement. The aorta was tortuous. The pleura was thickened on the right, and entrapped fluid was present in the lesser fissure.

The patient improved on a regimen of digitalization, salt restriction, and 15 mg. of erythrol tetranitrate four times daily. On the seventh hospital day the patient developed a picture of mesenteric artery occlusion and at an emergency operation a segment of terminal ileum and ascending colon was removed. An embolus had occluded a branch of the ileocolic artery. Later the same day an embolus was removed from the left common iliac artery. He left the hospital on the eleventh postoperative day on a program similar to the one maintained in the hospital.

The patient was followed in the out-patient department, where he reported that he was able to work as a dishwasher with only occasional episodes of pain, which were promptly relieved by nitroglycerin. His blood pressure was 155 mm. systolic and 95 diastolic on one occasion, and 124 mm. systolic and 90 mm. diastolic on another visit.

Four months after discharge the patient was found in his room in an unresponsive state.

On admission to the hospital he was stuporous but moved all extremities. There were marked cyanosis and irregular breathing. There was no odor of alcohol or acetone on his breath. The lungs were clear. The heart showed a diastolic gallop rhythm and a rate of 180. There was a grade 2 systolic murmur at the apex. The liver edge was felt three fingerbreadths below the costal margin and was slightly irregular. The reflexes were equal bilaterally except for absent abdominals.

The temperature was 98° F.; pulse rate, 180; respirations, 24. The blood pressure was 94 mm. systolic and 80 mm. diastolic.

The urine and blood, including the electrolytes, were normal. A lumbar puncture showed an initial pressure equivalent to 175 mm. of water, with normal dynamics. It caused some bleeding but the supernatant fluid was clear.

The patient remained stuporous and died four and a half hours after admission.

Autopsy Findings: The heart weighed 530 gm. Both ventricular walls were moderately thickened; the left measured 17 mm. and the right 6 mm. All four chambers were dilated. The endocardium was thickened throughout the heart and appeared gray and semitranslucent. This was most marked in the outflow tracts of the ventricles and in the atria. The myocardium was normal in appearance except for a small scar 1 cm. in diameter at the apex of the left ventricle. No abnormality of the valves was evident.

The coronary arteries had a normal distribution and were pliable and soft. The intima was smooth and pink, with no evidence of atherosclerosis.

The lungs were congested and edematous, weighing 1,500 gm. The other viscera were congested and there were 300 c.c. of clear ascitic fluid present. The ileocolostomy was intact and the left common iliac artery was patent.

Microscopic examination showed endocardial thickening caused by elastic and collagen fibers. This was patchy but at no point was it marked. Except for the scar at the apex there was no fibrous tissue replacement of the myocardium.

Microscopic study of other organs showed the changes of congestion and edema.

Comment

This second case, also over 50 years of age and with angina pectoris, bundle branch block and congestive heart failure, though of shorter duration than our first case (6 years' duration instead of 15), presents further evidence that this disease may occur in later life, last for years, but eventuate in death. It is of interest that both these patients came to autopsy within a few months in the same hospital.

BIBLIOGRAPHY

1. Gowing, N. F. C.: Congenital fibro-elastosis of endocardium, J. Path. and Bact. **65**: 13, 1953.
2. Blumberg, R. W., and Lyon, R. A.: Endocardial sclerosis, Am. J. Dis. Child. **84**: 291, 1952.
3. Letteer, C. R.: Endocardial fibroelastosis, Ann. Int. Med. **38**: 573, 1953.
4. Becker, B. J. P., Chatgidakis, C. B., and van Lingen, B.: Cardiovascular collagenosis with parietal endocardial thrombosis. A clinicopathologic study of forty cases, Circulation **7**: 345, 1953.
5. Thomas, W. A., Randall, R. V., Castleman, B., and Bland, E. F.: Heart disease of obscure etiology with special reference to endocardial fibroelastosis in the adult. A study of 20 autopsied cases, in preparation, 1953.
6. Averill, J. H., Randall, R. V., Joffe, E., and White, P. D.: Congestive heart failure with endocardial fibroelastosis in siblings, in press, 1953.

IDIOPATHIC INFARCTION OF THE OMENTUM: REPORT OF TWO CASES*

By Arthur Bauman, M.D., and Paul W. Hoffert, M.D., *Bronx, New York*

Since Eitel reported the first case of primary or idiopathic torsion of the greater omentum in 1899,[1] approximately 100 cases of torsion, with and without infarction, have been reported in the literature.[2] Thirty-six additional cases of primary segmental infarction without torsion have been described.[3-15]

With the exception of Eitel's patient, all of the patients presented the picture of an acute surgical abdomen. Since the symptoms and signs were usually confined to the right lower quadrant, the preoperative diagnosis was acute appendicitis in the majority of cases. In relatively few instances the preoperative diagnosis was either a perforated viscus or acute cholecystitis. The purpose of this report is to add two more cases to the literature, one with primary torsion and infarction of the omentum, and one with primary segmental infarction without torsion. In both instances the clinical picture simulated acute cholecystitis.

Case Reports

Case 1. A 24 year old Korean war veteran was admitted to the Veterans Administration Hospital, Bronx, N. Y., on October 25, 1952. Two days before admis-

* Received for publication October 14, 1953.
From the Medical and Surgical Services of the Veterans Administration Hospital, Bronx, N. Y.

sion the patient experienced the onset of diffuse crampy abdominal pain. Although severe at first, it subsided and the patient was able to sleep. On the following day the pain became localized to the right upper quadrant; it was aggravated by motion but did not radiate. No medical attention was sought until the following day when the pain increased. There was mild anorexia but no nausea, vomiting or diarrhea.

The patient had had an appendectomy performed in 1948. His Army service was not complicated by illness. Very careful questioning revealed that in his teens the patient had had rare episodes of mild epigastric pain relieved by food. These recurred in 1949 but he received no treatment.

Physical examination revealed a well developed and well nourished male in no distress but complaining of moderate right upper quadrant pain on movement. The blood pressure was 140/90 mm. Hg, the pulse 96 per minute, and the temperature 99° F. Positive findings were limited to the epigastrium, where there was marked tenderness just to the right of the midline. There was localized muscle guarding, and several examiners felt a globular mass immediately beneath the area of tenderness. The rest of the abdomen was soft. Peristalsis was active and the rectal examination negative. The white cell count was 10,850, with a normal differential. Serum amylase and lipase were normal. The urine was negative. A roentgenogram of the abdomen in the supine and upright positions did not reveal evidence of radiopaque calculi in the region of the gall-bladder or free air under the diaphragm. The bowel was not distended.

Course in Hospital: A presumptive diagnosis of acute cholecystitis was made, and the patient was placed on constant nasogastric suction with intravenous fluids and electrolytes. Because of the history of intermittent epigastric pain, he was started on an early ulcer diet on the following day. On October 27 the pain remained unchanged but the temperature rose to 102° F. Palpation during fluoroscopic examination of a barium swallow revealed a point of maximal tenderness in the right upper quadrant, distinctly lateral to a slightly hyperirritable duodenum. The patient was transferred to the surgical service with the diagnosis of acute cholecystitis.

On October 28, under general anesthesia, an exploratory laparotomy was performed through a right subcostal incision. Immediately beneath the middle of the incision an indurated hemorrhagic mass, well within the borders of the greater omentum, was noted. The mass proved to be a part of the omentum that had risen up and rotated about a pedicle. The involved omentum measured 6 by 10 cm. and was intimately attached to the anterior abdominal wall just beneath the right costal margin at the nipple line. The gall-bladder was grossly normal. It was thin-walled, emptied easily, and contained no calculi. There was slight scarring in the region of the duodenal bulb but no evidence of recent activity. Thorough exploration revealed no other intra-abdominal abnormality. The area of infarcted omentum was resected, the rent in the omentum repaired, and the wound closed in layers. The patient's postoperative course was not eventful and he was sent home symptom-free on the seventh post operative day.

Microscopic examination of the resected omentum showed hemorrhage and nonspecific granulation tissue. No antecedent pathology in the omentum or its blood vessels was seen either grossly or microscopically.

Comment on first case: We feel that this case is an example of idiopathic torsion and infarction of the omentum. That the bout of appendicitis and subsequent appendectomy four years prior to the present episode may have been etiologic factors is a possibility. It should be evident, however, that the involved omentum was a considerable distance from the site of previous disease. It is not likely that the minimally scarred duodenum played any part in the patient's present illness.

Case 2. A 31 year old white male was admitted to the Veterans Administration Hospital, Bronx, N. Y., on April 22, 1953, because of abdominal pain. Three days before admission the patient had noted the onset of a dull ache in the right upper quadrant which persisted unchanged until admission. There was no nausea, vomiting, anorexia or abnormal bowel movements. Review of systems was negative for any food intolerance or gastrointestinal disturbances.

Physical examination revealed a moderately obese white male in mild distress. The blood pressure was 150/110 mm. Hg, the pulse 120 per minute, and the temperature 101° F. There was direct tenderness and muscle guarding under the right costal margin. No mass was felt. The white cell count was 10,900, with 81 per cent polymorphocellular leukocytes. The urine was negative.

The initial impression was acute cholecystitis, and the patient received clear fluids by mouth and antibiotics. On this regimen his symptoms subsided and his temperature returned to normal. A cholecystogram was not remarkable.

On May 19 the patient was re-admitted for an exploratory laparotomy during a symptom-free period. Under general anesthesia, the abdomen was explored through a right subcostal incision. Anterior to the stomach a portion of infarcted omentum measuring 7.5 by 5.0 cm. was seen. This necrotic omental tissue was adherent to a loop of small bowel. There was no evidence of twisting. The involved omentum was dissected free and resected. The abdomen was otherwise negative. The wound was closed in layers and the patient was discharged on the seventh postoperative day. Pathologic examination of the specimen revealed foci of infarction and fat necrosis. The cause was not apparent.

Comment on second case: One can only speculate as to whether the infarcted omentum would have caused this patient difficulty at a later date had it not been resected during a symptom-free period. It is possible that some instances of unexplained small bowel obstruction are due to a previously unrecognized omental infarct which has become adherent to the bowel wall. A kinked area of bowel can then act as an axis about which twisting may occur. Schomberg [4] anticipated possible obstruction when he performed an ileotransverse colostomy in order to by-pass an omental infarct which had become adherent to the bowel in the ileocecal region.

Discussion

1. *Definition:* Primary or idiopathic torsion without infarction, infarction without torsion, and torsion with infarction are all situations where there is no evidence of a primary pathologic process in (a) the blood vessels of the omentum, (b) the omentum itself, (c) the abdominal wall, or (d) in any organ, abdominal or pelvic, which might embarrass the omentum secondarily. There has always been considerable controversy as to whether the presence of an inguinal hernia automatically rules out a primary omental disorder. It is easy to see how omentum can become twisted and infarcted when it is part of the hernia mass. Traction of any kind has been held as a likely cause of damage to the thin-walled veins of the omentum. Another theory holds that, by slipping into and out of a hernial sac, the omentum is lengthened; when the hernia is reduced, the now foreshortened omentum can, with relative ease, develop a pedicle about which to twist. Although this reasoning has merit we do not believe it is always valid, since a small asymptomatic potential hernia would not necessarily preclude the occurrence of primary omental pathology. Furthermore, torsion and infarction of the gastrohepatic omentum in an individual with an inguinal hernia would appear to be more

coincidental than causally related. Each case, then, must be assessed separately to determine whether it fits into the "idiopathic" group.

2. *Historical:* Eitel's case [1] of primary idiopathic torsion of the greater omentum was the first reported case of torsion unassociated with an inguinal hernia. Unlike all other cases where the presenting symptom was pain, Eitel's patient presented because of ascites for which a paracentesis was done. Since there was no infarction at laparotomy, the omentum was simply untwisted, with complete restoration of circulation and disappearance of symptoms. The following year in 1900, Wiener [16] reported a case of torsion and infarction of the omentum in a 79 year old male. Although complicated by the presence of a small, easily reducible, asymptomatic inguinal hernia, the involved omentum evidently bore no relationship to the hernia. In 1902, Baldwin [17] and Syme [18] each reported cases unassociated with hernia. Scudder's case [19] was complicated by appendicitis. Since then approximately 100 cases of primary omental torsion, with and without infarction, have appeared in the literature. Chronologically, the subject has been reviewed by McWhorter,[20] D'Errico,[21] Morris,[22] Anton et al.[23] and Leitner.[2]

Bush [24] reported a case of hemorrhagic infarction of the omentum in 1896, but the presence of a 435 gm. spleen and the likelihood of an underlying systemic disease would appear to eliminate this case from the idiopathic group. Schomberg [4] noted the first case of idiopathic segmental infarction in 1913. In 1919, Swain [3] published two cases of what he thought were instances of torsion and infarction, but laparotomy failed to disclose any evidence of torsion. Three more cases were added by Schomberg in 1919.[4] Johnson's case [25] is not acceptable since a herniorrhaphy scar fixed the omentum and there was arteriosclerosis of the omental vessels. Pines and Rabinovich [5] collected six cases from the files of the Jewish Hospital of Brooklyn. Of the 23 cases assembled by Cave,[11] only 20 can be considered idiopathic. Catanzaro and Farley [12] reported two children who had primary omental infarctions. The total number of authenticated cases, including eight recent additions,[9-15] plus our own, thus stands at 37.

3. *Etiology:*

A. *Torsion:* The mechanism for primary torsion is not understood. The majority of cases show involvement of the right lower border of the omentum. To explain this, Morris [22] and others have pointed out that the right border of the omentum is usually longer than the left, is more mobile, and is not infrequently composed of two or more tongues. In reviewing the literature, however, we find that the presence of multiple tongues has not been noted with any degree of frequency. An accessory omentum was implicated in only two of the 25 cases reviewed by McWhorter.[20]

Payr [26] pointed out that the omental veins are unusually long and tortuous and, once slightly kinked, become rapidly engorged with blood, while the artery, by becoming rigid, acts as a fulcrum and perpetuates the spiral rotation of the omental veins. In animal experiments, Payr first traumatized the omentum rather severely, then awaited the production of torsion. This sequence is the reverse of what is presumed to happen spontaneously in humans. One should not disregard the implication, however, since it is possible that in some cases of torsion and infarction of the omentum, infarction may have occurred first.

In 138 cases of primary and secondary torsion of the omentum reviewed by Morris [22] there were 31 cases in which there seemed to be a causal relationship

between trauma or physical exertion and the onset of symptoms. Falls, blows, whirling around, violent coughing, and even hyperperistalsis produced by catharsis have all been mentioned as etiologic factors in specific instances.[20] Of particular interest and of possible practical importance is a case where torsion reputedly occurred from failure to rearrange the omentum after a long operative procedure carried out with the patient in the Trendelenburg position,[22] but it is clear that such cases would fall into the secondary or non-idiopathic group. A previously unsuspected omentitis has also been postulated, but this is obviously speculative. Obesity has been mentioned as a factor in promoting or facilitating torsion, but the evidence is not convincing.

B. *Infarction without torsion:* It is even more difficult to account for primary segmental infarction of the omentum in the absence of torsion. That torsion may have been present prior to laparotomy is always a possibility. Pines and Rabinovich [5] contended that traction on the omentum from any cause could produce sufficient endothelial injury to foster clotting. Totten [27] proposed that vascular congestion due to sluggish blood flow, viz., after eating, might be a factor. Instances of primary infarction have been reported in patients with congestive heart failure. If this is presumed to be the cause, as in Berger's case,[28] one is impressed by the infrequent occurrence of thrombosis of omental veins in the presence of congestive failure when compared to thrombosis in other sites, namely, the leg veins. Leitner [2] cites instances of infarction precipitated by trauma. Finally, Hood and Geraci [15] have recently reported a case in which the greater omentum was suddenly caught in a triangular recess whose boundaries were the anterior surface of the liver, the falciform ligament, and the anterior abdominal wall.

4. *The Clinical Syndrome:*

A. *Age:* The youngest patient with torsion and infarction was one year old [20]; the oldest, if Wiener's case is accepted as an example of the primary form, was 79.[16] The youngest patient with idiopathic segmental infarction was four years old [12]; the oldest was 64.[5] The majority of patients in each group were between 25 and 55.

B. *Sex:* In considering all cases of torsion of the omentum, Morris [22] found that 90 per cent occurred in males. He attributed this to the greater incidence of inguinal hernia in the male. When corrected for the occurrence of hernia, the ratio was not strikingly different. Similarly, McWhorter [20] and D'Errico,[21] both of whom dealt with the primary form alone, noted that males predominated 20 to six and 22 to nine, respectively. Of all cases of primary segmental infarction of the omentum, 32 have occurred in males and only five in females.[3-15] There is no explanation for this difference between the sexes.

C. Symptoms: Pain is almost always present in both primary torsion and infarction and infarction without torsion. It may be gradual or abrupt in onset. At first it is usually diffuse, then localized, almost invariably to the right quadrant. Although some authors stress the paucity of gastrointestinal symptoms, anorexia, nausea, vomiting, diarrhea or constipation has been observed in 30 to 50 per cent of the cases. There is nothing characteristic about the temperature, which varies from normal values to 103° F.; the white cell count can be normal or twice normal, with a significant shift to the left. The duration of symptoms until laparotomy is performed varies from hours to three weeks, most patients undergoing surgery between one and four days after symptoms appear. Leitner [2] re-

ported a patient who had right upper quadrant pain, presumed to be gall-bladder disease, for 17 years before laparotomy disclosed torsion and infarction of the greater omentum; the gall-bladder was completely normal. Although repeated bouts of torsion without infarction may have explained the long history, the authors did not state that other pathology, such as a peptic ulcer or pancreatitis, had been ruled out. A mass may be palpable, but this finding is by no means constant. McWhorter's figure [20] of 30 per cent is somewhat high.

D. *Diagnosis:* To the best of our knowledge, D'Errico [21] is the only one who ever made the correct preoperative diagnosis of torsion and infarction of the omentum. He did this in 1931, a year after he reviewed the literature on the subject. Even in retrospect, there was nothing characteristic to warrant the diagnosis. None of the 37 cases of idiopathic segmental infarction was correctly diagnosed prior to surgery.

Acute appendicitis was the diagnosis in 19 of 26 cases of torsion and infarction reviewed by McWhorter,[20] 31 of 38 cases by Morris,[22] and 24 of 31 cases by D'Errico.[21] These same authors record that acute cholecystitis was the diagnosis in four, four and three cases, respectively. When a mass is palpable in the right upper quadrant, such as in one of the cases reported by Anton et al.[23] or Leitner,[2] the diagnosis of cholecystitis seems inescapable. Although acute cholecystitis was the first diagnosis mentioned in Leitner's fourth case, there was considerable doubt about the diagnosis. Interestingly enough, this patient, a 27 year old male, had torsion and infarction of the gastrohepatic omentum.

Including our own case, acute cholecystitis was thought to be the diagnosis in only three of 37 cases of idiopathic segmental infarction. In these,[2, 15] the clinical features clearly resembled acute cholecystitis. A mass was palpable in only one case.

In brief, there are no features distinctive of torsion, torsion and infarction, and infarction without torsion to warrant their diagnoses preoperatively. Idiopathic omental disease should be considered in the differential diagnosis of the acute abdomen, however, since it will stimulate the surgeon to examine the omentum carefully in every case where the cause of the acute abdomen is unclear even at laparotomy.

E. *Treatment:* The treatment is always surgical with an exploratory laparotomy. The involved omentum is usually excised. Schomberg [4] bypassed the involved omentum with an ileotransverse colostomy. Cagney and Milroy [30] drained the peritoneum of one patient, with prompt recovery. Rees and Pond [31] did not resect the omentum in two cases of what we regard as secondary infarction, since these patients had previously undergone extensive abdominal surgery. In the last three cases, no follow-up is available. Although the omentum has been untwisted when no infarction was present, D'Errico warned against this because of the possibility of recurrence, a situation that has never been reported. As stated previously, it is possible that certain instances of bowel obstruction might result from unresected lesions of the omentum. Notwithstanding the possible complications of any surgical procedure, the outlook is excellent.

Summary and Conclusions

1. One case of primary torsion and infarction of the greater omentum and one case of primary infarction without torsion of the greater omentum are reported.

2. Both cases simulated acute cholecystitis, the preoperative diagnosis in each case.

3. Idiopathic omental disease should be considered in the differential diagnosis of the acute surgical abdomen, since it will stimulate the surgeon to inspect the omentum very carefully whenever the cause of an acute abdomen is obscure.

4. It is conceivable that an organized omental infarct, by facilitating torsion of the bowel, may be responsible for some cases of bowel obstruction.

5. Certain historical, etiologic and clinical features of idiopathic omental infarction are reviewed.

BIBLIOGRAPHY

1. Eitel, G. G.: A rare omental tumor, M. Rec. **55**: 715, 1899.
2. Leitner, M. S., Jordan, C. G., Spinner, H., and Reese, E. C.: Torsion, infarction, and hemorrhage of the omentum as a cause of acute abdominal distress, Ann. Surg. **135**: 103, 1952.
3. Swain, J.: The diagnosis of torsion of the greater omentum, Bristol Med.-Chir. J. **37**: 202, 1919–1920.
4. Schomberg, H.: Akute hämorrhagische Epiploitis unter dem Bilde einer akuten Appendicitis, Beitr. z. klin. Chir. **146**: 89, 1929.
5. Pines, B., and Rabinovich, J.: Idiopathic segmental infarction of the greater omentum, Surg., Gynec. and Obst. **71**: 80, 1940.
6. Joss, C. S., and Pratt, J. H.: Primary idiopathic segmental infarction of the greater omentum, Minnesota Med. **31**: 996, 1948.
7. Seley, G. P.: Primary idiopathic segmental infarction of the greater omentum, J. Mt. Sinai Hosp. **17**: 523, 1951.
8. Higgins, G. A.: Idiopathic spontaneous segmental infarction of the omentum, Arch. Surg. **64**: 395, 1952.
9. Kerdasha, R.: Idiopathic spontaneous segmental infarction of the greater omentum, Ann. Surg. **137**: 419, 1953.
10. Tille, R. J.: Idiopathic segmental hemorrhagic infarction of the greater omentum, Ann. Surg. **138**: 279, 1953.
11. Cave, W. H.: Primary idiopathic infarction of the greater omentum, Illinois M. J. **101**: 130, 1952.
12. Catanzaro, F. P., and Farley, J. E., Jr.: Omental segmental infarction: two cases in children simulating appendicitis, J. Pediat. **40**: 240, 1952.
13. Graham, J. A., and Levenson, S. A.: Omental apoplexy: idiopathic segmental infarction of the greater omentum, Am. J. Digest. Dis. **17**: 114, 1950.
14. Sinow, G. S.: Idiopathic segmental infarction of the greater omentum, Am. J. Digest. Dis. **20**: 43, 1953.
15. Hood, R. T., Jr., and Geraci, J. E.: Infarction of the greater omentum simulating acute cholecystitis: report of case, Proc. Staff Meet., Mayo Clin. **28**: 296, 1953.
16. Wiener, J., Jr.: A contribution to the study of intra-abdominal omental torsion, Ann. Surg. **32**: 648, 1900.
17. Baldwin, J. F.: A contribution to the study of intra-abdominal omental torsion, Ann. Surg. **36**: 940, 1902.
18. Syme, G. A.: Case of intra-abdominal omental torsion, Intercolon. M. J. Australasia **7**: 444, 1902.
19. Scudder, C. L.: Intra-abdominal torsion of the entire greater omentum, Ann. Surg. **40**: 916, 1904.
20. McWhorter, G. L.: Torsion of omentum without hernia, Arch. Surg. **16**: 569, 1928.
21. D'Errico, E.: Primary torsion of the greater omentum, New England J. Med. **203**: 1181, 1930.

22. Morris, J. H.: Torsion of the omentum, Arch. Surg. **24**: 40, 1932.
23. Anton, J. I., Jennings, J. E., and Spiegel, M. B.: Primary omental torsion, Am. J. Surg. **68**: 303, 1945.
24. Bush, P.: A case of hemorrhage into the great omentum, Lancet **1**: 286, 1896.
25. Johnson, A. H.: The great omentum and omental thrombosis, Northwest Med. **31**: 285, 1932.
26. Payr, E.: Weitere experimentelle und klinische Beitrage zur Frage der Stieldrehung intraperitonealer Organe und Geschwulste, Deutche Ztschr. f. Chir. **85**: 392, 1906.
27. Totten, H. P.: Primary idiopathic segmental infarction of the greater omentum, Am. J. Surg. **56**: 676, 1942.
28. Berger, A. R.: Hemorrhagic infarction of the greater omentum, Arch. Surg. **36**: 497, 1938.
29. D'Errico, E.: Primary torsion of the greater omentum, New England J. Med. **205**: 1147, 1931.
30. Cagney, M. S., and Milroy, G.: Idiopathic infarction of the omentum, Brit. J. Surg. **35**: 95, 1947.
31. Rees, V. L., and Pond, V. M.: Obstruction of gastroenterostomy stoma due to thrombosis of omentum, Am. Surgeon **17**: 391, 1951.

REPORT OF A CASE OF PURPURA ANNULARIS TELANGIECTODES (MAJOCCHI'S DISEASE) AND ITS TREATMENT WITH CORTISONE*

By IRVING KASS, M.D., *Wadsworth, Kansas,* PHILIP SNEID, M.D., *Kansas City, Missouri,* and MANUEL SLAVIN, M.D., *Wadsworth, Kansas*

IN 1896 Domenico Majocchi [1] observed the unusual hemorrhagic eruption which now bears his name. He first noted this slowly progressing eruption on the lower part of the legs of a 21 year old man. He called this disorder "purpura annularis telangiectodes." The disorder was characterized by cutaneous hemorrhages or hemorrhagic puncta which coalesced to form purpuric and pigmented macules and rings of 2 to 20 mm. in diameter. These did not fade on pressure. The centers of many of the annular figures were smooth, depigmented and atrophic. Associated with the eruption were rheumatoid pains in the legs. The first record of a case of purpura annularis telangiectodes by an observer other than Majocchi was by Brandweiner in 1905.[2] In 1915 MacKee [3] presented his comprehensive articles on Majocchi's disease, and since then many patients have been demonstrated before dermatologic societies with the diagnosis of purpura annularis telangiectodes.[4, 5, 6, 7, 8]

Prior to cortisone therapy no medication was successful in controlling the cutaneous and systemic manifestations of the syndrome. It is felt that the rarity of the condition and the confusion surrounding the diagnosis, as well as the response to cortisone, justify this presentation of the clinical and histologic findings of Majocchi's disease.

* Received for publication October 12, 1953.
The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Case Report

This 41 year old Korean veteran was admitted to the medical service on May 12, 1953, because of a severe rheumatic pain in the right knee. Although the onset of this episode of pain was of recent origin, about seven months prior to the present hospital admission the patient had been treated in a military facility for a similar attack of pain. The symptoms were controlled with cortisone and in February, 1953, he was discharged from the Armed Forces with the diagnosis of rheumatoid arthritis. For at least seven years he had noticed an annular eruption of varying intensity on his lower extremities. At one time the diagnosis of psoriasis had been made. There was no history of a recent exposure to, or intake of, noxious agents, drugs, alcohol or vaccines.

Past History: As a child he had had measles, mumps, typhoid fever and chicken-pox. In 1948 he had a gonorrheal infection. There was no history of any allergic manifestations.

Family History: Noncontributory.

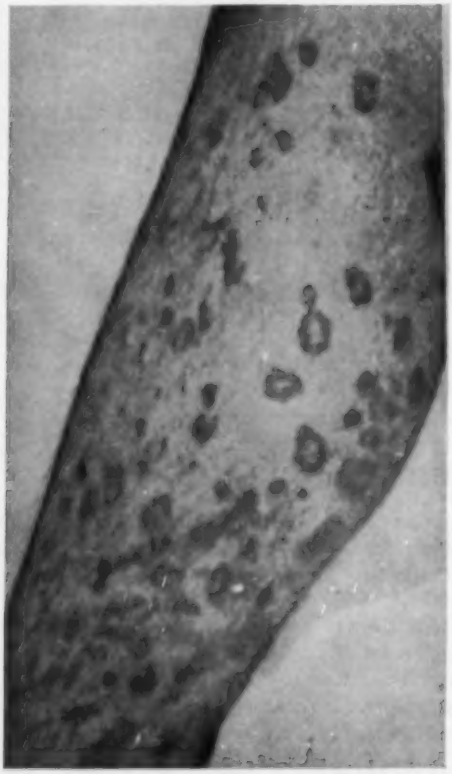


FIG. 1. Photograph shows the annular lesions of purpura annularis telangiectodes. Note the central atrophy and achromia present in some of the lesions (MacKee).

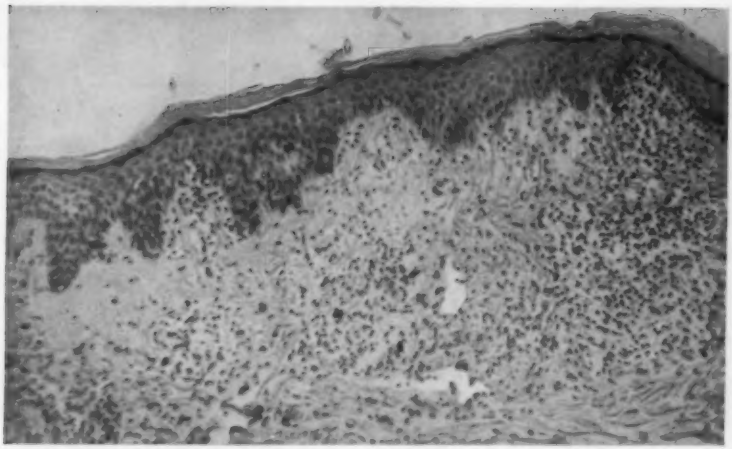


FIG. 2. Lesions prior to hormone therapy show a proliferation of the capillaries and connective tissue in the subpapillary layer. An infiltration consisting of leukocytes and lymphocytes can be seen. Obliterative changes are observed in some of the subdermal arterioles.

Physical Examination: Patient was a well nourished white male who did not appear to be acutely or chronically ill. Despite a marked limitation of motion in the right knee, there was no swelling or redness. Blood pressure 130/90 mm. of Hg in both arms; pulse, 105; temperature, 98.6° F. There were no significant eye, ear, nose or throat findings. Inspection, palpation and auscultation of the chest were all within normal limits. The heart was normal in size and shape. No murmurs were heard. The liver, kidneys and spleen were not palpable. Numerous dime-sized or smaller lesions were seen on the buttocks and the lower extremities. The lesions were purpuric and formed discrete rings. The color varied from rust to a livid red; in addition, punctate spots were visible. Mild blanching was noted on diascopic pressure. Some of the lesions showed minimal central atrophy and achromia. On the periphery of the rings fine, linear, discrete telangiectatic vessels were visible (figure 1). There was no infiltration of the skin or dermographia.

Laboratory Results: White blood cells, 8,600; normal differential; 84 per cent hemoglobin; sedimentation rate, 29; platelet count, 290,000; bleeding time, 2 minutes 45 seconds; clotting time, 12 minutes; prothrombin time, 100 per cent of normal. Clot retraction originally reported as slight was subsequently reported as good. Donath-Landsteiner and Ham tests were both negative. Red blood cell fragility: patient's initial hemolysis, 0.39 per cent; complete hemolysis, 0.30 per cent; control: initial hemolysis, 0.45 per cent; complete hemolysis, 0.33. The sternal marrow showed no noteworthy pathologic features. No lupus erythematosus cells were found in the marrow or peripheral smear preparations. Stools were negative for blood on three occasions.

Urinalysis: color, straw; specific gravity, 1.035; albumin, faint trace. Bence Jones protein was not found. Complement fixation for syphilis, negative. Uric acid, 3.8; nonprotein nitrogen, 36; glucose, 93; calcium, 6.4 mEq./L., inorganic phosphorus, 3.2; alkaline phosphatase, 3.2 Bodansky units; total protein, 6.7 gm. per cent; albumin, 4.5; globulin, 2.2; A/G ratio, 2; serum bilirubin, 0.5 mg. per cent;

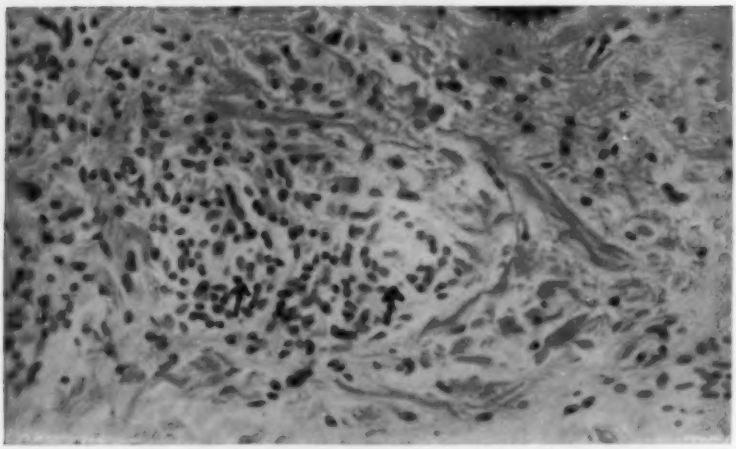


FIG. 3. Section of subpapillary arterioles shows an endothelial proliferation. There is a moderate perivascular infiltration but no evidence of hemorrhage.

total cholesterol, 160; esters, 60 per cent. Tuberculin test, intermediate strength PPD: negative. Histoplasmosis skin test, 1 plus after 48 hours. Coccidioidomycosis skin test, negative after 48 hours. Agglutinations for typhoid, para A & B, brucellosis, proteus OX19 and tularemia, negative.

A roentgenogram of the chest was within normal limits. Roentgenograms of both knees and ankles revealed a smooth articular surface without evidence of any bone productive or destructive changes. Roentgenograms of the dorsal spine demonstrated a slight scoliosis. There was no evidence of any arthritic involvement.

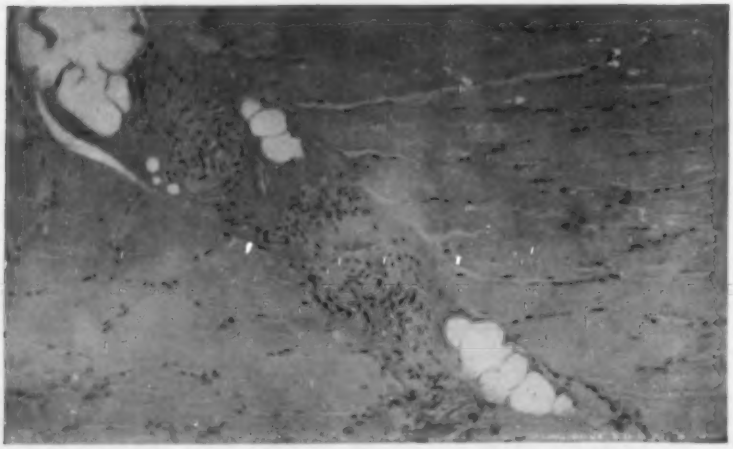


FIG. 4. Vessels of underlying muscle tissue show no adventitial changes.

Roentgenograms of the lumbosacral spine and sacro-iliac joints appeared to be within normal limits. A complete gastrointestinal series, including a gall-bladder study, was likewise within normal limits. Electrocardiogram with routine 12 leads was within normal limits.

Fifteen days after admission of the patient a skin and muscle biopsy was performed on the right leg. The pathologic changes were most conspicuous in the capillaries in the subpapillary layer. There was an increase in the number of these vessels. The vessels were dilated and congested with focal areas of perivascular edema and dilatations of the lymphatic spaces (figure 2). Some of the vessels showed definite thickening as a result of the endarteritis, with complete occlusion of a few. There was a moderate perivascular cellular infiltration but no evidence of hemorrhage (figure 3). No definite aneurysmal sacculation or necrosis of the vessel walls was visualized. Iron stains revealed small focal deposits of pigment in the subpapillary layer. The underlying muscle sections showed a normal striated muscle, and no adventitial changes were noted in the vascular structures (figure 4).

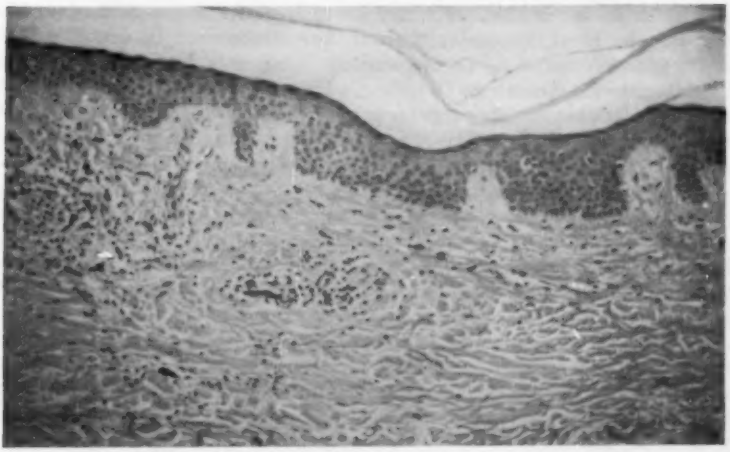


FIG. 5. Eight days following cortisone therapy, section showed a marked regression of the edema and perivascular infiltration.

Hospital Course: For about two weeks following the patient's hospitalization the rheumatoid complaint was treated conservatively. No improvement was noted. Patient was placed on oral cortisone therapy once the diagnosis was established. He was given 300 mg. of cortisone the first day and 200 mg. the second day, and was maintained on an oral dose of 25 mg. of cortisone four times a day for 10 days. Then the dosage of cortisone was gradually decreased. During the withdrawal period 15 mg. of ACTH were given intramuscularly four times a day. No withdrawal symptoms were observed. In addition to the cortisone, patient was given a high protein, low salt diet, 25 mg. of testosterone intramuscularly twice weekly, and 2 gm. of potassium chloride three times a day orally.

Three days after the therapy was initiated the cutaneous and joint manifestations began to subside and within 10 days were completely gone. Eight days after the hormonal therapy was started another skin biopsy was performed. The section showed a marked regression of the edema and perivascular infiltration with a sug-

gestion of a mild sclerosis of the connective tissue in the subpapillary layer. No discernible change could be noted in the degree of endarteritis (figure 5).

Case Summary: This is a case of Majocchi's disease which had previously been diagnosed as rheumatoid arthritis. The cutaneous lesions and joint symptoms both responded to cortisone therapy. No etiologic factor for the condition was disclosed.

Discussion

Majocchi observed that purpura annularis could be divided into three stages of clinical evolution: (1) the telangiectatic, (2) the hemorrhagic-pigmentary, and (3) the atrophic. Often there is an overlapping, so that the three stages are seen simultaneously. Occasionally, as noted by Brandweiner,[2] the atrophic phase is absent. The eruption usually begins in the form of punctate capillary ectasias and hemorrhages. Diascopic pressure effects only a partial blanching of the lesions. The color of the lesion varies from the usual bright red of the earliest stages to the darker red tint or rust color of the later stages. The individual lesions may be linear, macular or half circles, as described by Lipschutz,[9] but they are generally annular in configuration. They vary in size from a minute red punctum to the dimensions of a dime. Hyperpigmentation, varying in color from light to dark brown, often appears as a halo around the ring lesions. Usually after several months the eruptions subside, leaving a central atrophy and achromia. Alopecia in the affected area is frequently noted. Generally there is only one attack, although numerous instances of relapses and remissions have been recorded. The eruption usually appears first in the lower extremities, and is symmetrical in distribution. The appearance of the eruption is not infrequently preceded by rheumatic and neuralgic pains in the knees. The disease usually attacks young men, but it has been seen in children. There is an absence of palpable infiltration, and usually there is no pruritus.

Histologic changes do not affect the epidermis, but just beneath it the vessels are usually dilated, some showing aneurysmal distortion. Small cell infiltration, more abundant about the widely dilated vessels, is noted, and some of the subdermal arterioles show an obliterating endarteritis. In the later stages the infiltration is replaced by atrophy.[10]

Majocchi's disease must be differentiated from the following diseases[11]: (1) a peculiar, progressive pigmentary disease of the skin (Schamberg's disease)[12]; (2) angioma serpiginosum (Hutchinson),[13] and (3) pigmented purpuric lichenoid dermatitis (Gougerot and Blum.)[14] These appear to be closely related conditions and may be cutaneous variants of a single process in different degrees. It is characteristic of each of these disorders that the clotting time, bleeding time, thrombocyte count and other hematologic factors are within normal limits. Schamberg[12] in his original paper admitted the similarity of the condition he described to angioma serpiginosum. This view is shared by Wise and Pollitzer[15] and Meirowsky.[16] Clinically, Schamberg's disease has been described as the progressive development of patches of small reddish puncta, "grains of cayenne pepper," and brown to brownish pigmentation of the ankles, shins, dorsa of feet, knees and flexor aspects of wrists. It is asymptomatic.

Angioma serpiginosum appears as grouped, minute, copper-to-bright red puncta with peripheral extension to form circinate and serpiginous lesions with

clear centers. Although the eruption predominates on the lower extremities, it may be generalized. There is no purpura or pigmentation. The pigmented purpuric lichenoid dermatitis of Gougerot and Blum has been described as a discrete, pink to orange-red, slightly elevated papule 0.25 to 2 mm. in size, mostly on the lower extremities. Lesions may be pigmented in varying shades. Michelson and Laymon [17] do not feel that the pigmented purpuric lichenoid dermatitis of Gougerot and Blum can be differentiated from Schamberg's disease.

Purpura annularis telangiectodes, because of the more pronounced purpuric quality and more nearly constant tendency to show annular lesions with central atrophy, may constitute a morphologic entity somewhat different from the others. Microscopically, the obliterative endarteritis appears to be a distinguishing feature and, along with the degenerative changes in the hair follicles, coil and sebaceous glands, is seen only in Majocchi's disease. Moderate perivascular lymphocytic infiltration is a common microscopic finding except in Schamberg's disease, where a dense, lymphoid, polymorphonuclear and epithelioid cell infiltrate in the papillary and subpapillary layers, particularly above the sweat ducts, has been described. Hemosiderin pigmentation is usually present in Majocchi's and Schamberg's disease, but absent in angioma serpiginosum and pigmented purpuric lichenoid dermatitis.

Many constitutional affections have been reported in association with purpura annularis telangiectodes.[10] Among them may be mentioned cardiovascular disease, various disturbances of circulation, diabetes, hemochromatosis, arthralgias, tuberculosis, toxic manifestation from ingestion of drugs, infection of the tonsils and nasal sinuses, allergic respiratory infection, gonorrhea and syphilis. As stated by Becker,[18] "The rarity of generalized telangiectasia and the banality of the presumably causal conditions suggests an inherent predisposition."

Majocchi, and later Trawinski,[19] felt that purpura annularis telangiectodes was a hypersensitivity reaction, and they postulated that it was caused by the direct action of a toxin on the vessels just beneath the epidermis and within the subpapillary zone. Stokes [20] stated that cardiac disease, syphilis, infectious disease or any toxin or toxin-producing agent capable of exciting endothelial reaction and proliferation could serve as the basis for Majocchi's syndrome. Lier [21] described a case in which the inflamed tonsils were removed and the lesions regressed.

In the past the treatment of Majocchi's disease, although ineffective, consisted of bed-rest, elevation of the limbs, vitamin C, vitamin K, rutin and antihistaminics. Because the present concept of the pathogenesis of purpura annularis telangiectodes links it with hypersensitivity inflammatory manifestations, it was felt that a course of cortisone therapy might be helpful as a result of its documented usefulness in other such reactions.[22, 23, 24, 25]

Clinically, the cutaneous lesions and joint manifestations began to subside about three days after cortisone therapy was started. A biopsy taken eight days after hormonal therapy showed a marked decrease in the perivascular infiltration. The caliber of the involved vessels was too small to determine if there was any fibrosis secondary to healing, as described by Baggenstoss.[26] Further observations will have to be made before the effectiveness of cortisone therapy in Majocchi's disease can be accurately determined.

Summary

A case of purpura annularis telangiectodes (Majocchi's disease) has been presented.

1. Although Schamberg's progressive dermatosis, the angioma serpiginosum of Hutchinson and the pigmented purpuric lichenoid dermatitis of Gougerot and Blum are closely related conditions, purpura annularis telangiectodes of Majocchi, because of its more pronounced purpuric quality as well as its tendency toward annular lesions with central atrophy and achromia, probably constitutes a somewhat different morphologic entity.

2. The eruption is frequently associated with rheumatoid pains in the legs. The latter symptom is sometimes confused with rheumatoid arthritis per se.

3. No known etiology has been advanced, and it appears that the entity could be related to any stimulus capable of exciting an endothelial reaction and proliferation.

4. Although further observations will be necessary, cortisone appears to be effective in the treatment of Majocchi's disease.

Acknowledgment

We are indebted to Dr. George Miller MacKee, of New York City, for permission to use figure 1, inasmuch as our pictures of the cutaneous lesions were not of reproducible quality.

BIBLIOGRAPHY

1. Majocchi, D.: Sopra una dermatosi telangiectode non ancora descritta "purpura annularis," Gior. ital. d. mal. ven. Milano **31**: 263–264, 1896.
2. Brandweiner, A.: Purpura annularis telangiectodes, Wien. dermat. Gesellsch. Arch. f. Dermat. u. Syph. **77**: 122, 1905.
3. MacKee, G. M.: Purpura annularis telangiectodes, J. Cutan. Dis. **33**: 129–141 (Feb.); 186–208 (Mar.); 280–311 (Apr.) 1915.
4. Sulzberger, M. B., and Leider, M.: A case of diagnosis; angioma serpiginosum (Hutchinson's infectious angioma?) or purpura annularis telangiectodes (Majocchi?), Arch. Dermat. and Syph. **64**: 794, 1951.
5. Gross, P.: Purpura annularis telangiectodes? Radiodermatitis? Hemostasis dermatitis? Arch. Dermat. and Syph. **60**: 800, 1949. (Part I.)
6. Kelly, E. F.: Purpura annularis telangiectodes, Arch. Dermat. and Syph. **60**: 441, 1949.
7. Senear, F. E., and Caro, M. R.: A case for diagnosis (purpura annularis telangiectodes?), Arch. Dermat. and Syph. **54**: 617, 1946.
8. Randall, S. J., Kierland, R. R., and Montgomery, H.: Pigmented purpuric eruptions, Arch. Dermat. and Syph. **64**: 177, 1951.
9. Lipschutz, B.: Case of purpura annularis telangiectodes presented at a society meeting, but no details are given, Wien. dermat. Gesellsch., June 1, 1912.
10. Wise, F.: Purpura annularis telangiectodes (Majocchi) and progressive pigmentary dermatosis (Schamberg), J. Invest. Dermat. **5**: 153, 1942.
11. Moursund, M. P., and Hirschmann, V. R.: Telangiectasia macularis eruptiva perstans, Arch. Dermat. and Syph. **63**: 233, 1951.
12. Schamberg, J. F.: A peculiar progressive pigmentary disease of the skin, Brit. J. Dermat. **12**: 1, 1901.
13. Hutchinson, J.: A peculiar form of serpiginous and infective naevoid disease, Arch. Surg. London **1**: 275 (Apr.) 1889–1890, Plate IX.
14. Gougerot, H., and Blum, P.: Purpura angiosclereux prurigineux avec elements lichenoides (presentation de malade), Bull. Soc. franç. de dermat. et syph. **32**: 161, 1925.

15. Wise, F., and Pollitzer, S.: Angioma (infective angioma of Hutchinson): with a report of a very extensive case, J. Cutan. Dis. **31**: 725–739 (Oct.); 916–942 (Nov.) 1913.
16. Meirowsky, E.: Schambergsche Erkrankung, Suttonsche Erkrankung, Chloasma, *in* Jadassohn, J., Handbuch der Haut- und Geschlechtskrankheiten, Vol. 4, pt. 2, 1933, J. Springer, Berlin, p. 971.
17. Michelson, H. E., and Laymon, C. W.: Purpuric pigmented lichenoid dermatitis, Arch. Dermat. and Syph. **32**: 707, 1935.
18. Becker, S. W.: Generalized telangiectasia. A clinical study with special consideration of etiology and pathology, Arch. Dermat. and Syph. **14**: 387, 1926.
19. Trawinski, H.: Monatsh. f. prakt. Dermat. **1**: 45, 1912; cited by Stokes.[20]
20. Stokes, J. H.: Generalized telangiectasia in association with syphilis, with the pathological picture of peripheral vascular sclerosis, Am. J. M. Sc. **149**: 669, 1915.
21. Lier, W.: Possible etiology of purpura annularis telangiectodes, Arch. f. Dermat. u. Syph. **115**: 405, 1913.
22. Hench, P. S.: Reversibility of rheumatic and non-rheumatic conditions, Ann. Int. Med. **36**: 1, 1952.
23. Kass, I., Jackson, A., and Slavin, M.: Treatment of sarcoidosis with cortisone: a discussion as to its mode of action, Am. Pract. **4**: 503–509 (Aug.) 1953.
24. Kass, I., Jackson, A., and Slavin, M.: Sarcoidosis a hypersensitivity reaction. A discussion of three cases, to be published, J. Allergy.
25. Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Streeten, D. H. P., and McCracken, B. H.: Pharmacologic aspects of adrenocortical steroids and ACTH in man, New England J. Med. **248**: 232–244; 284–294; 323–337; 369–378; 588–601; 632–645, 1953.
26. Baggenstoss, A. H., Schick, R. M., and Polley, H. F.: The effect of cortisone on the lesions of periarteritis nodosa, Am. J. Path. **27**: 537, 1951.

CORTISONE THERAPY IN PORPHYRIA HEPATICA, ACUTE INTERMITTENT TYPE: A REPORT OF UNFAVORABLE RESULTS*

By O. Charles Olson, M.D., F.A.C.P., and Merritt H. Stiles, M.D., F.A.C.P., *Spokane, Washington*

It is not the purpose of this paper to review the clinical and pathologic features of porphyria, since they have been adequately covered in previous papers and these authors can add nothing further.

We do believe it is worth while, however, to review briefly a tentative classification of porphyria which has been recently suggested by Dr. C. J. Watson.[1] We believe that this classification will serve to clarify the clinical picture and to furnish a better understanding of the pathologic background of this disease.

Gunther proposed the first classification of porphyria many years ago (1911), but his nomenclature is conflicting and it has been difficult to classify all cases properly. Watson's first classification, (1) photosensitive, (2) intermittent acute, and (3) mixed, is quite useful from a clinical standpoint, but some cases that belong in the last category show no intermittent acute manifestations for long periods.

* Received for publication September 2, 1953.

TABLE I

Watson's New Classification of Porphyria

I. Porphyria erythropoietica
II. Porphyria hepatica
  1. Intermittent acute
  2. Cutanea tarda
  3. Mixed
  4. Latent

Watson [1] has recently proposed a newer classification, which is more basic and which we believe will be very acceptable (table 1).

The first type he calls *porphyria erythropoietica*. These cases demonstrate early photosensitivity, increased hemolysis, and erythropoiesis and splenomegaly. They show excessive and abnormal porphyrin formation in the bone marrow. This type is rare, less than six cases having been reported in the United States. Several of these cases have been treated by splenectomy, with encouraging results.

The second type is *porphyria hepatica*, in which the excessive formation of porphyrins, porphyrin precursors and related compounds takes place in the liver.

There are several subclassifications of porphyria hepatica. The intermittent acute type, with the chief clinical manifestations relating to the abdomen and nervous system, is most common. In the cutanea tarda type, photosensitivity is manifest sooner or later. The mixed type has elements of both preceding types.

We have two cases to present, both manifesting the acute, intermittent type of porphyria and both demonstrating an unfavorable response to treatment with cortisone.

CASE REPORTS

Case 1. This 21 year old white female was first admitted to the hospital on December 10, 1951, with an admitting diagnosis of porphyria, since she had recently been passing red urine and a younger sister had died of porphyria and diabetes mellitus two years previously.

The patient had noticed red urine for about three weeks prior to admission. She had been in normal health until November 15, 1951, at which time she complained of mild abdominal pain, cramping in nature. Slight constipation was noted. There were no other complaints, but the abdominal pain had continued up to the day of admission.

Physical examination revealed a slightly obese, somewhat euphoric white female, lying quietly in bed and responding well to questions. The pulse rate was 92 per minute, respiratory rate 24, temperature 98.0° F., and blood pressure 150/102 mm. of Hg. General physical examination was normal throughout, and the abdomen was soft, with no palpable masses. Complete neurologic examination was normal. The patient had not voided for nine hours and it was necessary to catheterize her intermittently until the fifth hospital day, at which time voiding began spontaneously. Laboratory findings were as follows: hemoglobin, 13.2 gm.; red blood cells, 4,152,000; white blood cells, 16,700, with 78 per cent segmented forms, 3 per cent bands, 12 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. A bromsulphalein dye test of liver function revealed 54 per cent retention at 30 minutes and 42 per cent retention at 60 minutes. A thymol turbidity test was reported as 5 units; the direct bilirubin was 0.7 mg. per cent and the indirect bilirubin, 0.48 mg. per cent. Carbon dioxide combining power, blood sugar and blood chlorides were all normal. Urine was of normal color until the third hospital day, when a

catheterized specimen was dark red in color and was reported as positive for porphyrins and porphobilinogen. Because of laboratory limitations the type of porphyrin found was not identified. Daily urines remained positive for porphobilinogen throughout the hospital stay.

Treatment was supportive in nature, including a high carbohydrate, high protein, low fat diet, vitamins, crude liver extract intramuscularly, and Demerol for pain. The patient improved somewhat, and was dismissed to the care of her local physician on December 23.

She was re-admitted to the hospital on January 1, 1952, because of severe abdominal pain, nausea and vomiting. She stated that the urine had been deep red in color for the preceding three days. It was noted that she had some clouding of the sensorium, although physical and neurologic examinations were again normal except for tachycardia of 140 per minute. Laboratory examination on the following day showed hemoglobin of 10.5 gm.; red blood cells, 3,810,000; white blood cells, 7,400 with normal differential. Urine was reported strongly positive for porphyrins and porphobilinogen. Blood glucose and chlorides were normal, but the blood urea nitrogen was 57 mg. per cent. The sedimentation rate was 119 mm. in one hour.

Because of the patient's persistent vomiting, it was necessary to resort to duodenal intubation and intravenous fluids. A gall-bladder x-ray was normal. Upper gastrointestinal x-ray showed marked gastric retention, with very little barium passing beyond the duodenal cap at the end of three hours. On January 8, seven days after admission, the patient first showed evidence of neurologic involvement. Definite weakness and incoördination were noted in the right arm and in both legs. Reflexes were slightly diminished in these extremities, but temperature, touch, pain and vibratory sensation were relatively normal. It was noted that the respiratory pattern was irregular and that breathing was mainly diaphragmatic. The urine continued to be strongly positive for porphyrins.

On January 9, because the patient had been deteriorating progressively and was semistuporous, cortisone was started in a dosage of 100 mg. intramuscularly every eight hours for three doses, then 100 mg. every 12 hours until January 22, when the dose was reduced to 75 mg. every 12 hours. This was continued until January 26, when the dosage was reduced to 50 mg. in the morning and 25 mg. in the evening. On February 6 the dosage was reduced to 25 mg. every 12 hours. Potassium chloride was given in a dose of 1 gm. three times daily.

During the first five days of cortisone therapy there seemed to be some improvement in the general condition and some return of muscular strength in the right arm and both legs, although marked general weakness continued. On the sixth day of cortisone therapy, while the dosage was still 100 mg. every 12 hours, the muscular weakness became very profound and the reflexes were greatly diminished. The patient's condition became progressively worse, and by January 29, after 20 days of cortisone therapy, she demonstrated a complete flaccid paralysis of all four extremities, with loss of all reflexes. Breathing was entirely diaphragmatic and weakness of the facial muscles was marked. The urine remained positive for porphyrins during the entire period.

On February 7, after cortisone had been reduced to 25 mg. every 12 hours, the patient had a slight remission and was able to move all four extremities, although with great effort. She continued to improve slightly for a period of five days, but on February 12 had a sudden return of the flaccid paralysis, with rapid deterioration of her general condition. She died on February 14, 1952.

Treatment in addition to the cortisone was entirely supportive and symptomatic. This patient, then, received a total dose of 4,775 mg. of cortisone over a period of 36 days.

Autopsy permission was not granted.

Case 2. This 26 year old female was first seen in June, 1951. She had been married for nine years and had two children, ages eight and three and one-half years, living and well. The chief complaints at the time of the first visit were weakness, fatigue, nervousness, infrequent menstruation and a weight-loss of 25 pounds during the preceding 16 months.

The patient stated that she had felt reasonably well, except during menses, until an attack of cramping abdominal pain in January and February, 1950. Because of this an exploratory laparotomy was performed, with the removal of the appendix, one ovary and one tube, and uterine suspension. Following the operation she had what she called a "nervous breakdown," requiring approximately four weeks of mental hospital care. She stated that there was a complete paralysis at this time, lasting about two months, followed by gradual improvement. Approximately six months later, while visiting in Nebraska, she had another "breakdown," requiring two and one-half months of hospitalization. In March, 1951, the symptoms again recurred and she was admitted to a mental hospital of her own volition. She had been released from the hospital approximately three and a half weeks before her initial visit to our office. As far as she knew, no definite diagnosis had been made at any time. She had continued to feel very tired and irritable, although she slept well. Marked anorexia was present. There had been amenorrhea since March. She stated that on occasion her urine had been dark red in color.

Initial physical examination revealed little of significance other than a tachycardia of 120 and a weight of 87 pounds, the height being 65½ inches. Routine laboratory studies were normal except for a moderately elevated sedimentation rate (45 mm., Westergren) and 3 plus albuminuria with innumerable casts. A specimen of urine after exposure to daylight turned dark red. A bromsulphalein test revealed 16 per cent retention at 30 minutes. Urinalysis revealed a positive test for porphobilinogen. Spectroscopic examination of the urine revealed the presence of coproporphyrin. A diagnosis of acute intermittent porphyria was made, and the patient was started on a low fat, high carbohydrate, high protein diet, with between-meal supplements. She was given dehydrocholic acid, one tablet three times a day after meals, and one therapeutic vitamin capsule three times a day. She improved very promptly, losing most of her symptoms and gaining about 16 pounds in weight during the next three months. The sedimentation rate fell to 18 mm. in one hour. The urine still remained strongly positive for porphobilinogen, however, and porphyrins were still present spectroscopically.

In October, 1951, there was another acute attack, requiring hospitalization of five or six weeks. Following this the patient improved slowly, the weight increasing gradually to 102 pounds.

The patient was next seen one year later, in October, 1952, with complaints of pain in the chest, back and abdomen which had started about 10 days previously, and with gradual increase in intensity. The pain was variable during the next seven weeks, several short periods of hospitalization being required. Treatment was symptomatic and supportive.

On December 4, 1952, the patient was again hospitalized because of severe anorexia and marked nervousness, associated with a moderate amount of abdominal pain. A bromsulphalein test at this time revealed 30 per cent dye retention at 30 minutes. Oral cortisone therapy was started on December 11, 150 mg. being given that day in divided doses, with 300 mg. during the next 24 hour period. There appeared to be slight improvement, with somewhat improved appetite. On December 13, 200 mg. of cortisone were given. The patient appeared somewhat euphoric and was much more active than she had been previously. She had a very restless night, with marked and increasing "nervousness." Part of the daily dosage of cortisone

was refused on that day, only 100 mg. being taken. On December 15 the patient was increasingly restless and started vomiting again. One hundred milligrams of cortisone were taken on this day.

On December 16 pain and restlessness definitely increased. There was increasing difficulty in getting the patient to take cortisone, and only 40 mg. were taken. On December 17, 50 mg. were taken. On December 18 the patient complained of difficult breathing and of marked weakness. The voice was quite faint. Marked tremor and foot drop were noted. No cortisone was given this day, but the patient was given 15 units ACTH by slow intravenous drip. On the next day the patient was unable to use her hands or feet; 15 units of ACTH were again given intravenously. On December 20 there was marked difficulty in swallowing, and the patient was unable to move her extremities. Deep tendon reflexes were absent. There was increasing respiratory difficulty, periodic cyanosis and inability to phonate. Respiratory distress gradually increased and the patient died at 2:30 a.m. on December 21. The total dosage administered was 950 mg. cortisone and 45 units ACTH over a period of 10 days.

Autopsy revealed acute generalized tracheobronchitis, moderate atrophy and fatty infiltration of the liver, chronic parenchymatous degeneration of the ganglion cells of the brain and spinal cord, chronic degenerative changes of the nerve fibers of the spinal cord, moderate parenchymatous degeneration and interstitial edema of the kidneys, and moderate atrophy and fatty changes of the bone marrow.

Comment

In the first case cited there seemed to be a somewhat favorable response during the first five days of cortisone therapy, but following this profound weakness developed, associated with areflexia, even though cortisone was still being administered in a daily dose of 200 mg. During the next two weeks complete flaccid paralysis developed. There was transient improvement after cortisone dosage was reduced to 50 mg. daily, but the flaccid paralysis subsequently returned with death on the thirty-sixth day of cortisone therapy.

Prior to the institution of cortisone therapy the second patient had run a prolonged course, with slow improvement in the mental symptoms and some improvement in the neurologic symptoms, which had been manifested in the form of paresthesias and weakness. There was still occasional abdominal pain radiating to the thighs, marked anorexia and marked asthenia. Steroid therapy was begun in the hope of improving the appetite and strength, and perhaps securing a remission. Because of the patient's uncoöperative attitude, which applied particularly to any type of parenteral medication, the cortisone was given orally. On the third day of this therapy there was a transient period of improvement, followed by a period of intense psychomotor activity, which in turn was followed by complete paralysis, with death ensuing on the tenth day after initiation of steroid treatment. During the period of psychomotor activity the patient refused any further oral medication, but the use of ACTH intravenously did not alter the course. The pattern of events in this case led to the opinion that cortisone and ACTH may have been important in precipitating the fatal outcome.

The search for a satisfactory method of therapy in porphyria of the acute intermittent type has been singularly unproductive. It is extremely difficult to evaluate carefully any method of treatment in a disease which has a natural tendency for remission and exacerbation; in addition, the study of a large series of

cases has been very difficult because of the relatively infrequent occurrence of the disease.

Dr. C. J. Watson,[1] at the 1953 convention of the American College of Physicians, reported on 15 cases treated with ACTH. Prompt and satisfactory remission took place in eight of these cases. Dr. Watson has been kind enough to comment on our cases, as follows:

"The situation with relation to ACTH or cortisone therapy in acute porphyria is not at all clear. There can be no doubt that some very dramatic remissions have occurred following the use of *brief* ACTH therapy. Our policy is not to continue it for more than five to seven days. I think that if any improvement occurs, it will occur within 48 to 72 hours at the outside. I am inclined now to the belief that the difference between relapse and remission in many cases of acute porphyria hangs on a very fine thread and that in not a few instances ACTH or possibly cortisone, though our experience has been entirely with ACTH, has some nonspecific effect in bringing about a remission. I cannot deny the possibility that in some instances it does cause worsening, although I have not seen any definite evidence of this myself, nor have I been able to find it in the few published cases in the literature. Nevertheless, I would agree that caution is necessary and that ACTH should be used only in relatively brief fashion, as above indicated."

Janoff [2] has recently reported a case of porphyria hepatica of the "mixed or cutanea tarda" type in a 39 year old woman. Forty units of ACTH gel were given every eight hours beginning on the fourth hospital day. Within a period of 24 hours a marked improvement in the clinical status was noted, and this continued on to a complete remission. She received a total of 1,050 units of ACTH gel over a period of 18 days.

Goldberg [3] has reported a case of acute porphyria in a 21 year old female treated with 12.5 units of ACTH every six hours for one week. He reported marked clinical improvement, even though ACTH was started late in the acute course. Total porphyrin excretion fluctuated widely during the period of ACTH administration. He cited experiences with other cases treated with ACTH leading to the conclusion that this hormone does not appreciably alter total porphyrin excretion.

Oltman [4] reported a case of acute porphyria in a 19 year old female. ACTH was given in doses of 20 units every six hours for eight days, without any change noted in the clinical condition and without any decrease in the total porphyrin excretion. ACTH was again given to this same patient three weeks later in an attempt to help the acute and severe abdominal pain. This time 20 units were given every six hours for five days, and then 25 units every six hours for five more days. There was no alleviation of the abdominal symptoms.

Gilbert, Toupin and Bell [5] reported using cortisone in a case of acute porphyria in a 34 year old male. The patient received a total of 5.75 gm. of cortisone in a period of 45 days. Total porphyrin excretion began to decrease immediately after beginning cortisone, reached a minimum on the fifth day of treatment, and remained at a low level during cortisone administration. Upon withdrawal of cortisone, the porphyrin excretion returned to the original high level. Unfortunately, phenobarbital had been inadvertently ordered shortly after the patient's hospital admission. It was discontinued four days after cortisone administration was begun. This coincided with the initial fall in porphyrin excretion. How-

ever, the cortisone therapy did not influence the clinical course or the fatal outcome in this patient.

Mellinger and Pearson [6] reported a case of acute porphyria in a 20 year old female treated with ACTH by slow intravenous drip. The first day she received 10 units and the second and third days 25 units each day, for a total dose of 60 units. No clinical improvement was noted, and there was no significant alteration in the urinary porphyrin excretion.

Conclusion

It is quite obvious, then, that up to this point there is no uniform opinion as to the effect of ACTH and cortisone in the treatment of porphyria hepatica. More detailed study is certainly needed. It is obvious that the use of cortisone in average doses must be approached with caution, but it is entirely possible that brief ACTH therapy started early in the acute phase may be very efficacious.

BIBLIOGRAPHY

1. Watson, C. J.: A basic classification of porphyria: certain diagnostic and therapeutic considerations, Read before the American College of Physicians in Atlantic City, New Jersey, April 13, 1953.
2. Janoff, L. A., Pouta, J. J., and Young, D.: Acute intermittent porphyria, prompt response to therapy with corticotropin, Arch. Int. Med. **91**: 389, 1953.
3. Goldberg, A., Macdonald, A. C., and Rimington, C.: Acute porphyria, experimental treatment with ACTH, Brit. M. J. **2**: 1174, 1952.
4. Oltman, J. D., and Friedman, S.: Acute porphyria, report of a case showing ineffectiveness of ACTH, New England J. Med. **244**: 173, 1951.
5. Gilbert, J. A. L., Toupin, H. M., and Bell, R. E.: Acute porphyria, Canad. M. A. J. **65**: 585, 1951.
6. Mellinger, G. W., and Pearson, C. C.: Acute porphyria: a case report, Ann. Int. Med. **38**: 862, 1953.

SYSTEMIC RETICULOENDOTHELIOSIS (LETTERER–SIWE DISEASE) IN THE ADULT MALE*

By Alton M. Paull, M.D., and Arthur M. Phillips, M.D.,
Providence, Rhode Island

It is now believed that the diverse manifestations of reticuloendotheliosis are merely different phases of one disease.[1, 2, 3, 4] The clinical picture produced depends on the rapidity of the pathologic process and the locations involved by the lesions. The more rapidly progressive and disseminated form described chiefly in infants and young children is characterized by generalized adenopathy, often hepatosplenomegaly, fever, purpura, anemia, cachexia and a fatal outcome.[5] Although rare, similar cases have been described in adults.[6, 7] The more chronic form of the disease usually evidences itself as either xanthoma disseminata of the skin, eosinophilic granuloma of bone, the Schüller-Christian

* Received for publication October 30, 1953.
From the Medical Service, Veterans Administration Hospital, Providence, Rhode Island.

syndrome, or as one of its variants. Transition from one clinical form to another has been observed,[5, 8, 9] tending to emphasize the importance of considering the various manifestations as part of one disease process. Lesions, apparently local and benign at their onset, such as eosinophilic granuloma of bone or xanthoma disseminata of the skin, may develop into acute or chronic reticuloendotheliosis, although from the literature this is apparently not usual.

The pathologic picture has been divided into different phases based on morphologic appearance.[5, 9] In the early lesions there is, predominantly, proliferation of round monocytic histiocytes with accumulation of eosinophils and the appearance of giant cells. This is followed by increase in blood vessels and fibroblasts. Cell necrosis and hemorrhage may be seen. If the process extends for some time, accumulations of intracellular lipid may become evident within the histiocytes and giant cells, giving a "foamy" appearance to their cytoplasm. With special preparations, double refractile lipoid droplets or crystals can be demonstrated. Following cell necrosis these may be seen extracellularly. In the fibrous phase the xanthoma and endothelial cells are gradually replaced by fibroblasts and connective tissue. There is considerable overlap of the various phases, so that in a given lesion one may see an indiscriminate arrangement of fibrous connective tissue, fibroblasts, some foam cells and also extracellular lipid deposits. The cholesterol content of the tissues is high, both in the acute and in the chronic form. However, the serum cholesterol is usually normal. The local accumulation of cholesterol is felt to be caused by new formation within the reticulum cells and not by infiltration from without.[1, 5, 9]

The various organs that may be involved are skin, bone, lymph nodes, liver, spleen, brain, dura, lung and pleura, either singly or in combination.[9] Lesions in the skin [9] manifest themselves as nodules, which may be isolated or grouped together and at times are pedunculated. They are usually slightly raised smooth patches with a yellow-maroon or dark brown color. The patches are irregular in shape and size and made up of individual lesions not much larger than a pinhead. They appear most often in the axilla, the sides of the neck and antecubital fossa. Pruritus is absent. Petechia-like areas may be present in the generalized form of the disease. In infants the xanthoma is a discrete, elevated brown-to-orange-colored lesion occurring not in clusters but singly. The size varies from pinhead to that of about a centimeter. As the infant grows older the xanthoma frequently disappears. The mucous membranes may also be involved, and hoarseness may result from lesions in the larynx.

Areas of involvement in the bone may produce pain or a mass, although often no local symptoms are present. The x-ray appearance is that of an osteolytic lesion with well defined borders. In rare cases there may be a moth-eaten appearance to the bone. The locations involved include the skull, vertebrae, pelvis, ribs and long bones. Pathologic fractures may occur, as well as penetration into joints. In the Schüller-Christian syndrome the characteristic defects are seen in the membranous bones (although others may also be involved). The bone lesions of eosinophilic granuloma are the sole manifestation of the disease and often heal spontaneously. They are sensitive to x-ray therapy.

Enlargement of lymph nodes, liver and spleen may be produced by the occurrence of granulomatous lesions. Whether hypersplenism occurs as a result of the splenomegaly is not clearly established but is suggested by some of the cases

reported by Scott and Robb-Smith,[6] where cytopenia was present together with a hyperplastic marrow and an enlarged spleen. Liver function is not impaired, as the lesions are focal.

Lesions occurring in the brain and dura may produce a variety of abnormalities, such as convulsions, paralyses and ataxia. Involvement of the hypothalamus, its pathways to the pituitary, or the posterior pituitary itself, may result in diabetes insipidus, such as is seen in the Schüller-Christian syndrome.

In the lung the disease may cause such symptoms as dyspnea and cough. Dullness and râles may be present on examination. Small patchy areas of infiltration are visible by x-ray, with an appearance similar to miliary tuberculosis or pneumoconiosis in some instances. Fibrosis of these granulomatous areas may produce pulmonary insufficiency and cor pulmonale.

In diffuse reticuloendotheliosis the peripheral blood may show cytopenia. Focal areas of granuloma formation in the bone marrow are present. The possible rôle of hypersplenism in the production of the abnormality in the hematopoietic picture has already been alluded to.

The following two cases represent systemic reticuloendotheliosis in adult males. In view of the relatively few such cases in the literature, it is felt that they may contribute to general awareness of the clinical picture.

Case Reports

Case 1. A 40 year old white male was admitted to the Veterans Administration Hospital, Providence, Rhode Island, on January 5, 1953, with the chief complaint of a constant lower back pain of seven months' duration. He had been well until July, 1952, when he developed "stiffness" of the lower back. One week later he developed a slight productive cough, coryza, sneezing and a sharp pain accentuated by deep breathing and coughing in the left anterior chest. He was treated by his physician for pleurisy. He recovered from this in a short time but continued to complain of a moderate amount of pain in the lower back. He continued to work as a stock clerk until Thanksgiving, 1952, when he again had a recurrence of the left pleuritic chest pain. He again recovered and continued working until December 5, 1952, when he suddenly began to vomit. He continued to vomit intermittently for the next nine days, losing 23 pounds. At this time the pain in the lower back became more severe. Two weeks prior to admission he developed "shooting pains" down both legs and again left pleuritic pain.

Past History: Patient had served with the U. S. Army in New Guinea for 32 months. He received a service-connected disability of 20 per cent for gunshot wounds of the legs and a nervous condition.

Review of Systems: Patient complains of having had a chronic cigarette cough for several years.

Physical Examination: Temperature, 100.2° F.; pulse, 100; respirations, 20; blood pressure, 135/70 mm. of Hg. Patient was a well developed, fairly well nourished white male, lying in bed and appearing chronically ill. There was a bilateral conjunctivitis. Funduscopic examination revealed increased tortuosity of the vessels. The right eardrum was scarred. The teeth were carious. Examination of the heart and lungs was negative. The liver and spleen were not palpable, and there was no lymphadenopathy. The peripheral arteries were pipe-stemmed. There was tenderness to pressure over the left rib cage. The remainder of the physical examination was not remarkable.

Laboratory Data: Hemoglobin, 11.3; hematocrit, 33; white blood cells, 5,400: 61 per cent polys, 28 lymphs, 6 monocytes, 4 eosinophils and 1 basophil. Urinalysis:

specific gravity, 1.012; albumin, 3 plus; occasional red blood cell; 2 to 4 white blood cells per high power field, and occasional fine granular and hyaline casts. Serology, negative; blood urea nitrogen, 39 mg. per cent; total protein, 5.4 gm. per cent; albumin, 2.8; globulin, 2.6. (Several urine specimens showed slight traces of Bence Jones protein.) Calcium, 10.3; PO_4, 4.2; chlorides, 75 mEq.; CO_2, 31 mEq.; alkaline phosphatase, 6.1 Bodansky units. Congo red test, negative. Serum sodium, 141 mEq/L. Serum potassium, 4.3 mEq/L. Cholesterol, 380 mg. per cent. Cephalin flocculation, negative. Thymol turbidity, 2 units. Serum bilirubin, 0.6 mg. per cent. Phenolsulfonphthalein, 20 per cent excretion in two hours. Total lipids, 0.945 gm.

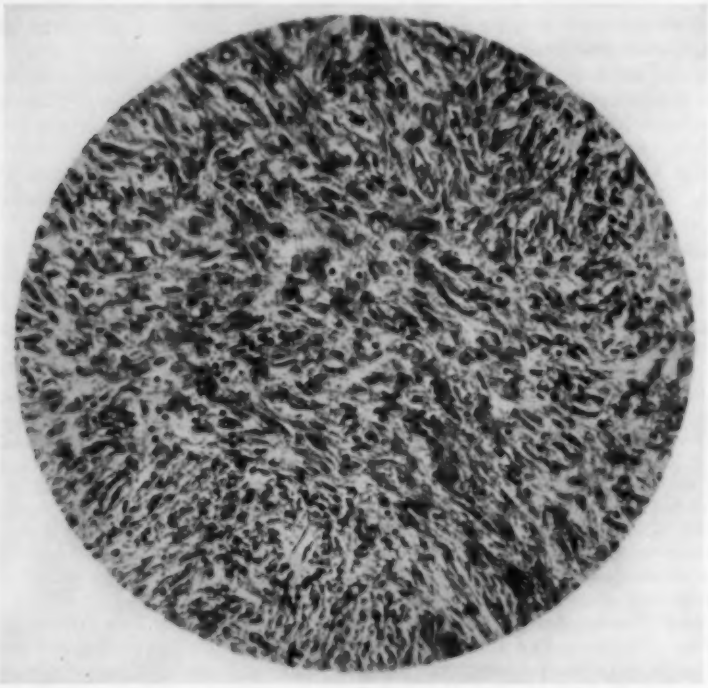


FIG. 1. Microscopic section (220 ×) showing complete replacement of the bone marrow with atypical spindle-like cells arranged in a solid pattern and whorls.

per cent. Phospholipids, 5 mg. per cent. Blood cultures, sterile. Stool culture, negative.

X-Ray Data: X-ray of dorsolumbar spine revealed partial collapse of the body of D11. There were a number of suspicious areas of rarefaction in the ribs, but none was definitely circumscribed. A number of sharply circumscribed areas of decreased density were seen in the alar portions of the pelvis, particularly in the supra-acetabular regions bilaterally. Chest: suspicious areas of decreased density were noted in the ribs. Skull: examination disclosed multiple circumscribed areas of rarefaction of from 4 to 12 mm. in diameter. Gastrointestinal series, negative.

Course in Hospital: It was initially thought that the patient had multiple myeloma. His course was progressively downward, and was characterized by repeated bouts of vomiting and intractable pain in his back and chest. Two sternal aspirations were unsuccessful, and a trephine biopsy was performed. The sections were consistent with a diagnosis of acute reticuloendotheliosis (figure 1). The patient was treated at different times in the next six months with x-ray therapy, nitrogen mustard, urethane, cortisone and Terramycin, without demonstrable benefit. He was unable to tolerate urethane in significant dosage due to gastrointestinal symptoms.

In June he returned to the hospital following a three week period at home during which he had progressively lost the use of his legs. Examination showed paraplegia, with lower motor neuron paralysis and atrophy of the muscles of his legs and thighs. Fasciculations were present and sensation was intact. X-rays showed progressive increase in the osteolytic areas in the skull, ribs, vertebrae and long bones. Progressive anemia (hemoglobin, 8.3 gm.; red blood cells, 2.5 million; hematocrit, 24) and azotemia (blood urea nitrogen, 131 mg. per cent) were evident. He died on July 16, 1953, in a cachectic condition, with deformity of his chest and in severe pain. At no time was hepatosplenomegaly, adenopathy or fever noted.

Autopsy (Dr. Richard Singer): At postmortem examination the body measured 62 inches and weighed approximately 90 pounds. The thorax was distorted by nodularity and depression of the ribs irregularly along the midclavicular and parasternal lines. The abdomen was scaphoid, and the skin over the entire abdomen was covered with petechial hemorrhages. There was atrophy of the liver and heart and hemosiderosis of the lungs, liver and spleen. The aorta and coronary vessels showed extensive atheromatous changes. The gall-bladder, extrahepatic biliary channels, small and large intestines, pancreas, ureters, bladder, seminal vesicles, prostate and portal venous system were not abnormal. The adrenal cortices were depleted of lipid. No remarkable lymph nodes were noted in the axillae, retroperitoneum or elsewhere. The kidneys each weighed 50 gm. They were remarkably shrunken and the capsules stripped with ease, revealing smooth, pale, light brown surfaces. Section through the kidneys revealed a light brown, pale parenchyma, the cortices averaged 4 mm. in thickness. The corticomedullary junctions were somewhat indistinct, though they could be made out. The pyramids were fairly well defined, and the minute dots of the nephron could be noted in the reflected light. The pelves were lined by pale gray mucosa. Sections through several ribs showed the marrow to be replaced completely by rubbery, homogeneous gray-brown tissue which was very pale and had a pink tint. The cortices of the ribs were shell-like, and the ribs could be cut with a knife without excessive pressure. Most of the ribs were deformed by protuberances, and sections from these sites showed replacement of the marrow cavity by this firm, rubbery, pink-gray homogeneous tissue, resembling tumor. In each instance, the cortices of the bone involved were very thin, with the consistency of brown paper, and all these bones could be cut with a knife. No evidence of tumor was noted except in the bone marrow grossly. The sternum also showed similar marrow changes, as described in the other bones above. The calvarium was eburnated, and cut with the usual resistance. It did not appear to be infiltrated with the tumor tissue, as described in the other bones.

Microscopic Description: Sections through the vertebrae, sternum and ribs showed a similar histologic picture (figure 1). There was complete absence and destruction of the bony trabeculae and most or all of the cortical bone, depending upon the bone involved. The marrow space was completely replaced by somewhat atypical spindle and sometimes polyhedral cells, arranged in a solid pattern and in whorls. Occasionally there was a tendency towards palisading, but this was not consistently true in all sections. Many small vascular channels were noted throughout the tumor tissue. The nuclei of these spindly and sometimes polyhedral cells were oval and

elongated, sometimes pale blue and sometimes dark blue. Nucleoli were frequent, prominent and large. A few mitotic figures were noted, but these were not bizarre. Special stains revealed a fair amount of collagen to be present sporadically in no definite pattern throughout the atypical neoplastic tissue. Stains for amyloid were negative. The tumor itself had a glossy appearance focally in rib sections, but these stained for collagens and not for amyloid. Stains for fat showed no fat in the neoplastic cells. A very rare tiny fat globule was noted which was extracellular. A few scattered eosinophils and other inflammatory cells were noted, but these were

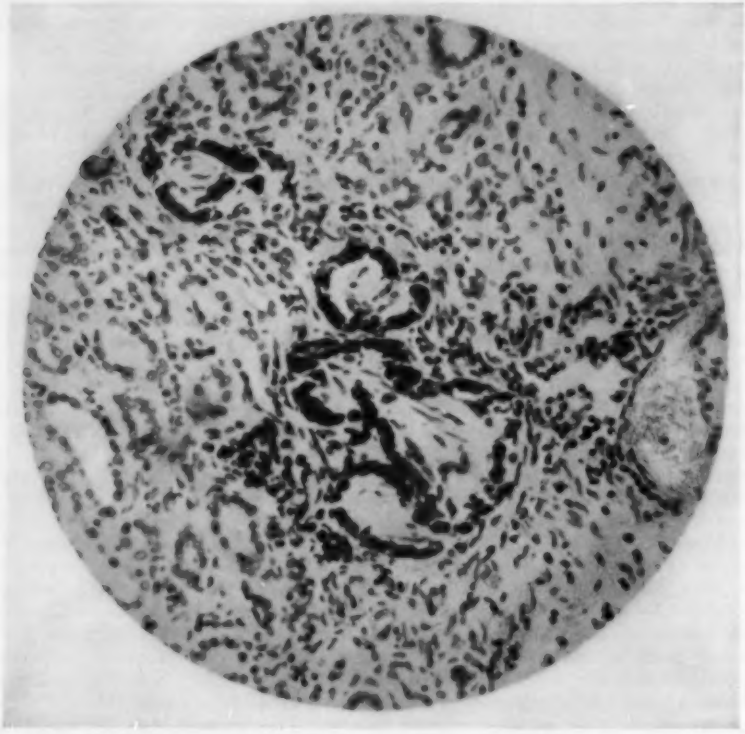


FIG. 2. Microscopic section (220×) showing a very dense and diffuse calcification of the tubular epithelium, principally of the convoluted tubules.

sparse and definitely not a feature. No hematopoiesis was noted throughout any of the marrow sections. Section through one parathyroid showed a large gland composed mostly of chief cells with scattered oxyphil cells in no regular pattern. Some secretion was noted focally. The architecture of the kidneys was normal. The glomeruli were intact, although somewhat ischemic. There was a very dense and diffuse calcification of the tubular epithelium, principally of the convoluted tubule (figure 2). This was a prominent change, and was marked in all sections. In addition, there were superficial scars radiating toward the pyramidal apices which were

thin and showed condensation of tubuli in these areas. Section through two axillary lymph nodes showed partial replacement by fibrous tissue.

Case 2. This was a 30 year old white male floral designer of Italian extraction whose illness began December, 1951, with fever, chills and sore throat. His fever continued despite treatment with Aureomycin, penicillin and sulfadiazine. Examination disclosed an alert, tense white male with a temperature of 101° F., a spleen two fingerbreadths below the costal margin, and a firm mass in the right lower quadrant. Blood count, urine, serology, serum bilirubin, thymol turbidity, serum calcium and potassium, alkaline phosphatase, blood cultures, and agglutinations for brucella, typhoid, paratyphoid and heterophil antibodies were normal. Electrocardiogram was normal. Chest x-ray was negative. X-ray study of the abdomen showed an enlarged spleen and a cystic area on the left pubic bone. Pyelography indicated mesial displacement of the right ureter, due to retroperitoneal mass. Gastrointestinal series and barium enema were negative.

Course in Hospital: The patient was thought to have lymphoma, and was given a course of x-ray therapy to the mass in the right lower quadrant, which subsequently decreased in size. He was febrile during the greater part of his hospital stay.

Second Admission: He returned eight months later (August 18, 1952) because of recurrence of fever. Examination again showed enlargement of the spleen. The mass formerly felt in the right lower quadrant was not palpable. He was essentially symptom-free and afebrile while in the hospital.

Third Admission (January 12, 1953): He returned again because of recurrence of fever, ranging from 101° to 104° F. daily. In the interim (from November to December, 1952) he had been studied elsewhere and found to have splenomegaly and anemia, and an exploratory laparotomy with biopsy of a retroperitoneal lymph node and liver was done. Scattered lipoid-laden histiocytes were seen in the portal areas of the liver, and the lymph node showed diffuse overgrowth of reticuloendothelial cells, lipoid-laden cells, and single and multinucleated giant cells in areas of inflammation. The pathologic diagnosis was Letterer-Siwe disease. Blood counts showed leukopenia, and granulocytic hyperplasia of the bone marrow was found on sternal aspiration. A course of nitrogen mustard was given, following which his appetite and sense of well being returned and his fever subsided. Physical examination showed a chronically ill male with splenomegaly. Hemoglobin, 9.6; white blood cells, 1,450; 66 per cent polys.

Course in Hospital: The patient ran an intermittent fever of Pel-Ebstein type; treatment with cortisone was not helpful. X-ray was begun over spleen but was discontinued because of a drop in the white blood cells. Later he was given nitrogen mustard (24 mg.), without striking benefit.

Final Admission (July, 1953): The patient had continued downward, with intermittent fever, weight loss, anorexia, anemia and leukopenia. Physical examination showed a chronically and acutely ill white male with pallor, splenomegaly and purpura.

Laboratory Data: Hemoglobin, 3.8 gm.; white blood cells, 2,100; 68 per cent polys; hematocrit, 15; bilirubin, 1.2 mg. per cent; urine urobilinogen, 1:100; fecal urobilinogen, 560 Ehrlich units per 100 gm.; reticulocytes, 0.5 per cent.

Course in Hospital: X-rays of chest, ribs and spine were normal. Course was progressively downward, with fever, wasting, anemia and leukopenia. No benefit was demonstrable from ACTH therapy given in the last six days of illness.

Discussion

Although these two patients were suffering from the same disease process, the clinical manifestations were quite dissimilar in many aspects. Case 1 ex-

hibited marked skeletal involvement, with resulting severe bone pain in both the chest and the back, extensive osteolytic areas visible by x-ray, and deformity of thorax evident on examination. The paraplegia present late in the course was felt to be a result of collapse of his vertebral framework. The extensive nephrocalcinosis responsible for his renal insufficiency was an accompaniment of prolonged hypercalciuria attendant upon the extensive skeletal demineralization. Unfortunately no determinations of urine calcium were done, although the serum levels of calcium and phosphorus were normal. Hyperplasia of the parathyroid glands was seen at autopsy. His clinical picture closely resembled multiple myeloma, with the bone pain and osteolytic lesions, the anemia, the renal insufficiency and Bence Jones proteinuria. However, normal antibody titers (usually deficient in multiple myeloma),[10] absent hyperglobulinemia and unsuccessful sternal aspiration were clues that another disease was responsible for the picture. The nature of this was developed by the sternal biopsy and, later, the autopsy.

The second case was similar to those reported previously in the literature [6, 7] in that fever, splenomegaly, adenopathy, purpura and anemia were major findings. Intermittent fever, splenomegaly and an abdominal mass were the presenting findings, with leukopenia, anemia and weight loss developing later. There was considerable evidence on his last admission of the development of a hemolytic anemia. This, together with the leukopenia in the peripheral blood and a marrow showing granulocytic hyperplasia, is suggestive of hypersplenism. This patient's clinical picture resembled malignant lymphoma until the histologic diagnosis was made.

Neither patient appeared to derive particular benefit from the various agents used in therapy, with the exception of the decrease in size of the right lower quadrant mass in case 2 following local x-ray therapy.

The cases provide no clue to the nature of the disease except that their course was similar to that of neoplasia. They do, however, reëmphasize the diverse manifestations that may occur. Recently attention has been called to the possible rôle of infection in the pathogenesis of the disease, with several apparent cures reported in children following antibiotic therapy. Fisher [8] reported a case in a two year old colored male whose blood cultures and tissue cultures grew *Paracolon Arizona* and whose recovery was attributed to therapy with Terramycin and Chloromycetin. Other cases responding to antibiotics have been noted by Bierman et al.[11] and Aronson.[12] The agents used were streptomycin, Aureomycin, Chloromycetin and penicillin. The results in our cases are at variance with these reports. Case 1 received 2 gm. of Terramycin daily for 18 days, and case 2 received at various times Aureomycin, penicillin, sulfadiazine and Terramycin. No beneficial effect on the course of the disease was noted.

Summary

1. Two cases of systemic reticuloendotheliosis (Letterer-Siwe disease) in adult males are described. Clinically, one resembled multiple myeloma and the other malignant lymphoma. Case 1 was of further interest because of the unusual complication of nephrocalcinosis and secondary hyperparathyroidism.

2. The protean nature of the disease is emphasized by their clinical dissimilarity.

3. The results of treatment with various recommended therapeutic agents were disappointing.

BIBLIOGRAPHY

1. Wallgren, A.: Systemic reticuloendothelial granuloma; nonlipoid reticuloendotheliosis and Schüller-Christian disease (relation to Letterer-Siwe's disease), Am. J. Dis. Child. **60**: 471–500, 1940.
2. Gross, P., and Jacox, H. W.: Eosinophilic granuloma and certain other reticuloendothelial hyperplasias of bone. A comparison of clinical, radiologic, and pathologic features, Am. J. M. Sc. **203**: 673–687, 1942.
3. Malloy, T. B.: Diseases of bone, New England J. Med. **227**: 955–960, 1942.
4. McCullough, N. B.: Eosinophilic granuloma with multiple osseous soft tissue lesions in an adult, Arch. Int. Med. **88**: 243–251, 1951.
5. Freud, P.: Evaluation of systemic reticuloendotheliosis in childhood, J. Pediat. **38**: 744–769, 1951.
6. Scott, R. B., and Robb-Smith, A. H. T.: Histocytic medullary reticulosis, Lancet **2**: 194–198 (July 22) 1939.
7. Asher, R.: Histiocytic medullary reticulosis: case without lymphadenopathy, Lancet **1**: 650–651 (May 4) 1946.
8. Fisher, R. H.: Multiple lesions of bone in Letterer-Siwe disease, J. Bone and Joint Surg. **35-A**: 445–464, 1953.
9. Thannhauser, S. F.: Lipoidosis—diseases of cellular lipid metabolism, 1950, Oxford University Press, New York.
10. Unpublished data.
11. Bierman, H. R., Lanham, J. T., Dod, K. S., Kelly, K. H., Miller, E. R., and Shimkin, M. B.: The ameliorative effect of antibiotics on non-lipoid reticuloendotheliosis (Letterer Siwe disease) in identical twins, J. Pediat. **40**: 269–284, 1952.
12. Aronson, R. P.: Streptomycin in Letterer-Siwe's disease, Lancet **1**: 889–890, 1951.

ACUTE HEMOLYTIC ANEMIA COMPLICATING INFECTIOUS MONONUCLEOSIS: REPORT OF TWO CASES*

By David H. Appelman, M.D., and George B. Gordon, M.D.,
Brooklyn, New York

The development of acute hemolytic anemia during the course of infectious mononucleosis has only recently been reported.[1-4] Dameshek and Schwartz[5] had previously reported the occurrence of hemolytic anemia in a patient with infectious mononucleosis but in this instance, sulfadiazine had been administered. Ellis, Wollenman and Stetson[1] described the occurrence of acute hemolytic anemia in an illness resembling infectious mononucleosis in which autohemagglutinins, hemolysins and a positive Donath-Landsteiner test were found. In their case the heterophil antibody titer was markedly elevated initially, as were the hemagglutinin titers. Coincident with the fall in the heterophil antibody titer a decrease in serum hemagglutinins was demonstrated. Wilson, Ward and Gray[3] reported a case of infectious mononucleosis and hemolytic anemia. Sawit-

* Received for publication November 4, 1953.
From the Department of Medicine, The Beth-El Hospital, Brooklyn, N. Y.

sky, Papps and Wiener [4] observed another case of acute hemolytic anemia complicating infectious mononucleosis. By the use of the Coombs' reagent, autosensitization of the patient's red cells was demonstrable during the hemolytic phase of the disease.

Case Reports

Case 1. A 21 year old white single male college student was admitted to the Beth-El Hospital on July 21, 1952. He had been ill for two weeks with sore throat, fatigability, weakness, anorexia, fever and enlargement of the cervical glands. Fever had ranged from 100° to 102° F. The past history, apart from measles and mumps in childhood, and family history were noncontributory. The use of drugs or sera prior to admission was denied except for one injection of penicillin and 2 gm. of Aureomycin taken orally during the first week of the illness.

Physical examination on admission disclosed a moderately pale, feverish white male with slightly icteric skin and sclerae. Rectal temperature was 103° F. The pharynx was injected. Numerous easily removable small white plaques were found on the tongue, gums and cheeks. Slightly tender lymph nodes, varying from pea to almond size, were palpated in the posterior cervical, submaxillary and anterior cervical areas. The liver and spleen were not palpable. No other significant findings were noted.

Laboratory: Hemoglobin, 7.6 gm. (55 per cent); red cells, 2.8 million; white cells, 7,000; neutrophils, 25 per cent; eosinophils, 1 per cent; monocytes, 4 per cent; lymphocytes, 70 per cent. Many of these lymphocytes were atypical and characteristic of infectious mononucleosis. Platelets numbered 300,000 per cubic millimeter. Reticulocytes numbered 7 per cent on the third hospital day and 8 per cent one week later. No abnormality in the structure of the red blood cells was noted. The red blood cell fragility test was normal. A sternal marrow aspiration revealed a granulocytic-erythrocytic ratio of 50:50. Megakaryocytes were normal in number, and the granulocytic elements were made up of 30 per cent myelocytes, 15 per cent metamyelocytes, 35 per cent segmented neutrophils and 20 per cent staff neutrophils. An increase in erythroblasts was noted.

The heterophil agglutination test was positive in a dilution of 1:2048. The Davidsohn exclusion test confirmed the diagnosis of infectious mononucleosis. The Coombs' test was negative on two occasions. The urinary urobilinogen was 1:20. No bile was found in the urine. Blood chemical examinations showed an icteric index that ranged from 16.6 to 25.3. The total serum bilirubin varied from 1.14 to 1.8 mg. per 100 c.c., and the direct serum bilirubin from 0.4 to 0.81 mg. per 100 c.c. Total serum proteins were 7.1 gm. per 100 c.c., with an albumin of 3.9 gm. per 100 c.c. and a globulin of 3.2 gm. per 100 c.c. Serum total cholesterol was 127 mg. per cent and the free cholesterol was 94 mg. per cent. The urea nitrogen, sugar, chlorides, sodium, potassium, alkaline phosphatase and carbon dioxide combining power were normal. The cephalin flocculation was 3 plus and the thymol turbidity was 4.5 units.

The electrocardiogram revealed mild myocardial changes which reverted to normal one week later.

Twenty-five milligrams of ACTH were administered intravenously in 500 c.c. of glucose in distilled water daily for five days. Each infusion was given over a 10 hour period. A rapid improvement of the throat lesions, lymphadenopathy and toxicity ensued. However, the icterus and anemia persisted. The patient was discharged from the hospital on August 9, 1952, with a hemoglobin of 60 per cent, 2.9 million erythrocytes and 8 per cent reticulocytes; quantitative serum bilirubin was 1.3 mg. per cent.

Follow-up examinations revealed a gradual rise in hemoglobin and red blood cells, accompanied by decreasing serum bilirubin level and reticulocyte counts. On November 11, 1952 the hemoglobin was 15.6 gm., with a red blood cell count of 5,140,000. Leukocytes were 5,050 per cubic millimeter, of which 49 per cent were segmented neutrophils, 3 per cent staff neutrophils, 46 per cent lymphocytes and 2 per cent eosinophils. The patient was asymptomatic and had returned to full activity.

Comment on Case 1: Following the report of the laboratory findings, it became apparent that the patient had both infectious mononucleosis and hemolytic anemia. The diagnosis of infectious mononucleosis was supported by the lymphadenopathy, positive heterophil agglutination test and the lymphocytosis with atypical lymphoid cells. However, the presence of jaundice, anemia, reticulocytosis and an erythroblastic marrow indicated that hemolytic anemia also existed. Dr. M. Morrison, the hematologist, concluded from peripheral blood and bone marrow studies that this was infectious mononucleosis with hemolytic anemia. It can be assumed that the hemolytic anemia occurred as a complication of the infectious mononucleosis, since the history did not indicate any preëxisting hemolytic disease, and recovery from the hemolytic phase followed subsidence of the infectious mononucleosis.

Case 2. A 22 year old white single male was admitted to the Beth-El Hospital on September 30, 1946. He gave a five week history of weakness, fatigability, sluggishness and "rust-colored" urine. Jaundice and fever appeared in the fourth week of illness. He was hospitalized following a fainting spell. Past history was negative except for an appendectomy in 1943 and furunculosis successfully treated with penicillin while he was in Germany in 1945. No history referable to malaria or other tropical diseases was elicited.

On his admission the patient was slightly asthenic, with icteric skin and sclerae. The pharynx was injected, and small discrete lymph nodes were scattered throughout the neck. The spleen was palpable 4 cm. below the costal margin. Rectal temperature was 103° F. No other significant findings were noted.

Laboratory examinations on the morning following his admission were: hemoglobin, 4.3 gm. (28 per cent); red blood corpuscles, 1.4 million, and 8,800 leukocytes per cubic millimeter. The differential count showed 70 per cent lymphocytes, 28 per cent segmented neutrophils and 2 per cent staff neutrophils. Atypical lymphocytes characteristic of infectious mononucleosis were seen. About 25 per cent of the red blood corpuscles were spherocytic. A marked anisocytosis was present. Reticulocytes numbered 7 per cent. Five normoblasts per 100 white blood cells were found on the blood smear. Platelets numbered 390,000 per cubic millimeter. Bleeding time, coagulation time, clot retraction time and prothrombin time were normal. A sternal marrow aspiration revealed a granulocytic-erythrocytic ratio of 50:50. Megakaryocytes were normal in number, and the granulocytic elements were made up of 35 per cent myelocytes, 35 per cent segmented neutrophils, 10 per cent metamyelocytes and 20 per cent staff neutrophils.

The heterophil agglutination test was positive in a dilution of 1:512. The red blood corpuscle fragility test with hypotonic saline solutions showed initial hemolysis at 0.48 per cent and complete hemolysis at 0.42 per cent. (With normal blood, hemolysis usually begins in the tube containing 0.44 or 0.42 per cent salt solution and is complete in the tube containing 0.34 per cent salt solution.) The urine was strongly positive for urobilinogen. Bile, hemosiderin and hemoglobin were absent from the urine.

Blood chemical examinations showed an icterus index of 15, a delayed van den Bergh reaction and a serum protein of 7.1 gm. per cent. The albumin was 3.9 gm.

per cent and the globulin was 3.2 gm. per cent. Serum total cholesterol was 100 mg. per cent and the cholesterol esters were 125 mg. per cent. The urea nitrogen, sugar and chlorides were normal. The cephalin flocculation test was 3 plus.

The Kline test was negative. Blood cultures showed no organisms. Repeated fecal examinations failed to reveal any parasites or ova. No malarial parasites were found in the bone marrow and peripheral blood specimens. The patient was Rh positive and group "O." Agglutination tests for brucellosis, typhoid, paratyphoid A and B, and typhus fever were negative.

Roentgenologic examination of long bones and chest was normal. The basal metabolic rate was plus 18. Fragility tests done on the blood of the patient's relatives were within normal limits and no cytologic abnormalities were found.

The patient was given 3,500 c.c. of blood during the first week of hospitalization. The hemoglobin rose to 5.5 gm. (36 per cent), with a red blood cell count of 1.9 million. The other hematologic and biochemical examinations were relatively unchanged. The urinary urobilinogen reached a titer of 1:100.

Two weeks after admission of the patient, additional laboratory examinations were done; tests for cold agglutinins, for paroxysmal hemoglobinuria by Mackenzie's modification [6] of the Donath-Landsteiner test, and for Marchiafava's disease by the Ham and Horack [7] procedure were all uniformly negative. The heterophil agglutination test was positive in a dilution of 1:256. The Davidsohn exclusion test confirmed the diagnosis of infectious mononucleosis.

The clinical course during the 10 weeks of hospitalization was uneventful. The temperature returned to normal on the twelfth day, after reaching a peak of 104° F. 48 hours after admission. The lymphadenopathy persisted. The spleen became barely palpable. A slight icteric tint to the skin was still perceptible on discharge.

Laboratory examinations carried out during the last week of hospitalization showed a hemoglobin of 9 gm. (58 per cent), with a red blood cell count of 2.8 million. Leukocytes were 7000 per cubic millimeter, of which 52 per cent were segmented neutrophils, 4 per cent eosinophils, 42 per cent lymphocytes and 2 per cent monocytes. No atypical lymphocytes were seen. A few macrocytes and an occasional spherocyte were seen on the stained blood smear. Reticulocytes were 3 per cent, and the platelets numbered 380,000 per cubic millimeter. Sternal marrow showed a granulocytic-erythrocytic ratio of 60:40. Granulocytic series showed 20 per cent neutrophilic myelocytes, 10 per cent eosinophilic myelocytes, 12 per cent metamyelocytes, 15 per cent staff neutrophils and 5 per cent eosinophils. The icterus index was 17. Quantitative serum bilirubin was 0.8 mg. per cent. The heterophil agglutination test was negative. The red blood cell fragility test had returned to normal. Initial hemolysis began at 0.44 per cent and was completed at 0.32 per cent. The urinary urobilinogen was positive in a dilution of 1:100.

There was nothing in the patient's history prior to the onset of the infectious mononucleosis to indicate a preëxisting hemolytic disease. The subject was not seen again until 18 months after discharge. He looked well and had no icterus, and the spleen was not palpable. Laboratory examinations at this time were: hemoglobin, 15.4 gm. (100 per cent); red blood corpuscles, 4.6 million, and 6,000 leukocytes per cubic millimeter. The differential count showed 51 per cent segmented neutrophils, 10 per cent staff neutrophils, 33 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. No pathologic cells were seen. Reticulocytes numbered 1.5 per cent, platelets 450,000 per cubic millimeter. Bleeding and coagulation times were normal. The heterophil agglutination test was negative. The red blood corpuscle fragility test with hypotonic salt solution showed initial hemolysis at 0.44 per cent and complete hemolysis at 0.34 per cent. Blood chemical examinations showed an icterus index of 4.3 units, a negative cephalin-cholesterol flocculation test and a zinc

turbidity test of 6.2 units. Bile, hemoglobin and hemosiderin were absent from the urine. The urinary urobilinogen was within normal limits.

Comment on Case 2: The lymphadenopathy, splenomegaly, lymphocytosis with atypical lymphoid cells and the positive heterophil agglutination test confirmed the diagnosis of infectious mononucleosis. The jaundice, anemia, increased red blood cell fragility to hypotonic salt, spherocytosis, increased urinary urobilinogen and erythroblastic marrow revealed that acute hemolytic anemia was also present. There was nothing in the patient's history prior to the onset of the infectious mononucleosis to indicate a preëxisting hemolytic disease. Infectious hepatitis might be considered as a possible diagnosis, but cases of infectious hepatitis almost invariably show an increased resistance to hypotonic saline.

Discussion

Infectious mononucleosis is usually a benign, self-limited disease requiring only symptomatic therapy. However, with the new peak of attention now being enjoyed by this disease, it can no longer be properly regarded as a diagnostic curiosity or as a benign and unimportant disorder. The disease may impair vital organs, frequently incapacitates and occasionally kills. Occasionally, serious complications such as hepatitis, thrombocytopenia, myocarditis, central nervous system involvement and splenic rupture may develop. Several fatal cases have been described, with death due to splenic rupture or to central nervous system involvement.[5, 9] In most patients the leukocyte picture is the only cytologic change of any significance. One of its outstanding features is the lack of anemia. However, a few cases with anemia and/or thrombocytopenia have been reported. Reed and Helwig [10] reported 300 cases of infectious mononucleosis, of which three presented severe anemia associated with a marked reduction of the white blood cells and platelets. The authors considered this pancytopenia to be part of the infectious mononucleosis. The complication of acute hemolytic anemia is rare but does occur.[1-4] The importance of recognizing that hemolytic anemia can occur during the course of infectious mononucleosis lies in its therapeutic implications. A noted hematologist examined the second patient and, after confirming that he had both hemolytic anemia and infectious mononucleosis, wrote that the patient's only hope for recovery lay in splenectomy. The realization that acute hemolytic anemia may occur as a complication of infectious mononucleosis and will disappear coincident with the fall in the heterophil antibody titer makes the consideration of splenectomy unnecessary in such patients.

There is no specific treatment for infectious mononucleosis. ACTH has been reported [11] to be beneficial in seriously ill cases of infectious mononucleosis. Treatment of the first patient with ACTH did result in rapid improvement.

Summary

Acute hemolytic anemia, although rare, does occur as a complication of infectious mononucleosis. Recovery from the hemolytic phase follows recovery from the infectious mononucleosis. Further clinical trial in severe or complicated cases of infectious mononucleosis is necessary to evaluate the specificity as well as the effectiveness of ACTH in the treatment of this disease.

BIBLIOGRAPHY

1. Ellis, L. B., Wollenman, O. J., and Stetson, R. P.: Autohemagglutinins and hemolysins with hemoglobinuria and acute hemolytic anemia in an illness resembling infectious mononucleosis, Blood **3**: 419, 1948.
2. Appelman, D. H., and Morrison, M. M.: Concomitant infectious mononucleosis and hemolytic icterus, Blood **4**: 186, 1949.
3. Wilson, S. J., Ward, C. E., and Gray, L. W.: Infectious lymphadenosis (mononucleosis) and hemolytic anemia in a Negro, Blood **4**: 189, 1949.
4. Sawitsky, A., Papps, J. P., and Wiener, L. M.: The demonstration of antibody in acute hemolytic anemia complicating infectious mononucleosis, Am. J. Med. **8**: 260, 1950.
5. Dameshek, W., and Schwartz, S.: Acute hemolytic anemia, Medicine **19**: 231, 1940.
6. Mackenzie, G. M.: Observations on paroxysmal hemoglobinuria, J. Clin. Investigation **7**: 27, 1929.
7. Ham, G. C., and Horack, H. M.: Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, Arch. Int. Med. **67**: 735, 1941.
8. Dolgopol, V. B., and Husson, G. S.: Infectious mononucleosis with neurological complications, report of a fatal case, Arch. Int. Med. **83**: 179, 1949.
9. Wintrobe, M. M.: Clinical hematology, 1951, Lea and Febiger, Philadelphia.
10. Reed, J. T., and Helwig, F. C.: Infectious mononucleosis. An analysis of 300 cases with three characterized by rare hematological features, Arch. Int. Med. **95**: 376, 1945.
11. Doran, J. K., and Weisberger, A. S.: The use of ACTH in infectious mononucleosis, Ann. Int. Med. **38**: 1058, 1953.

EDITORIAL

SOME OBSERVATIONS ON THE PATHOGENESIS OF CARDIAC EDEMA

EDEMA is a simple little word of humble Greek origin; and that is as far as edema walks with humility and simplicity. Its pathogenesis now presents one of the most complex problems in pathophysiology and many theories have already foundered in the uncharted sea of edema fluid. If among the complexities of today's concepts there is one trend towards simplification, it is that attention is now focused on one central mechanism, salt retention, as the *fons et origo* of most types of edema; whereas a decade or so ago it was customary to ascribe different mechanisms to different types of edema with little or no pathogenetic overlap. Not that knowledge of salt retention is as new as it seems, for fully half a century ago French writers were well aware of its importance in edema formation.

Naturally much the greatest volume of work on the mechanism of edema formation has been done on the commonest edematous syndrome, congestive heart failure. It is not the purpose of this review to present a complete survey of the many hundreds of contributions that have been made to this subject in recent years. Since our traditional ideas of congestive failure were formidably challenged a decade or so ago, numerous authors, approaching the subject from various viewpoints, have contributed useful critiques to which reference can be made.[1-10]

BACKWARD FAILURE

The backward failure theory—or hemodynamic sequence, as Homer Smith [11] prefers to call it—is based on Starling's principles [12] and postulates as the prime initiator of edema the piling up of blood in the venous system under high pressure behind the failing heart-pump. This simple concept fails, however, to account for a number of the observed features of congestive failure; among these may be mentioned:

(1) The blood volume is increased and there is hemodilution; whereas a primary increase in venous and capillary pressures with transudation

[1] Paine, R., and Smith, J. R.: The mechanism of heart failure, Am. J. Med. **6**: 84, 1949.
[2] Merrill, A. J.: Mechanisms of salt and water retention in heart failure, Am. J. Med. **6**: 357, 1949.
[3] Bradley, S. E., and Blake, W. D.: Pathogenesis of renal dysfunction during congestive heart failure, Am. J. Med. **6**: 470, 1949.
[4] McMichael, J.: Cardiac venous congestion. Its causes and consequences, Am. J. Med. **6**: 651, 1949.
[5] Richards, D. W.: Dynamics of congestive heart failure, Am. J. Med. **6**: 772, 1949.
[6] Starr, I.: Our changing viewpoint about congestive failure, Ann. Int. Med. **30**: 1, 1949.
[7] Smith, H. W.: The kidney, 1951, Oxford Univ. Press, N. Y., pp. 663-693.
[8] Peters, J. P.: The problem of cardiac edema, Am. J. Med. **12**: 66, 1952.
[9] Schaaf, R. S.: Cardiovascular diseases. A review of some significant publications (July 1949-June 1952), Arch. Int. Med. **93**: 430-435, 1954.
[10] Bruger, M.: The pathogenesis and differential diagnosis of edema, Med. Clin. N. Am. **38**: 875, 1954.
[11] Smith, H. W.: The kidney, 1951, Oxford Univ. Press, N. Y., p. 666.
[12] Starling, E. H.: Physiological factors involved in the causation of dropsy, Lancet **1**: 1405, 1896.

should cause hemoconcentration. Warren and Stead [13] precipitated congestive failure in compensated cardiacs by feeding salt and withholding diuretics and showed clearly that increase in blood volume and hemodilution together with gain in weight occurred *before* any significant rise in venous pressure developed.

(2) High cardiac outputs, well above normal, may be observed in frank congestive failure ("high output failure").

(3) Spontaneous changes in urine flow observed in patients with moderate congestive failure are not preceded or accompanied by any consistent changes in right auricular pressure.[14] Changes in venous pressure therefore cannot be considered the primary cause of the disturbed water balance that characterizes congestive failure.

(4) The elevated venous pressure of congestive failure persists after death.[15]

In the experimental animal moreover, it has been shown that virtual destruction of the right ventricle leads to no demonstrable increase in venous pressure.[16]

Forward Failure

Today heart failure is sometimes defined without referring to the heart at all; thus "a metabolic state in which the essential abnormality is an abnormal retention of salt, in consequence of which water is retained and a state of hyperhydration results." [17] In fact, recent trends in investigation and theory have led to the waggish comment that the current aim is to prove that the heart has nothing to do with heart failure. Like all good hyperboles, this one lies without deceiving.

The train of events now widely accepted as the most probable sequence in congestive failure may be summarized as follows. The normal heart responds to exertion by an increased output equal to the metabolic demands. When myocardial insufficiency sets in, cardiac reserve dwindles and when the now inadequate heart is called upon for extra work it cannot quite meet the metabolic requirements—the output may increase, but not quite in proportion to demand. In such circumstances there is an emergency redistribution of blood in which the kidneys suffer disproportionately; for when cardiac output is halved, renal blood flow may be reduced to as little

[13] Warren, J. V., and Stead, E. A.: Fluid dynamics in chronic congestive heart failure. An interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, Arch. Int. Med. **73**: 138, 1944.

[14] Brod, J., and Fejfar, Z.: The origin of oedema in heart failure, Quart. J. Med. **19**: 187, 1950.

[15] Starr, I.: Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies, Am. J. M. Sc. **199**: 40, 1940.

[16] Starr, I., Jeffers, W. A., and Meade, R. H.: The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog with a discussion of the relation between clinical congestive heart failure and heart disease, Am. Heart J. **26**: 291, 1943.

[17] Gold, H., in Conferences on Therapy: Most effective application of therapeutic measures in the management of congestive failure, Am. J. Med. **16**: 118, 1954.

as one fifth.[18] This reduction is apparently effected by constriction of the *efferent* arterioles because, while the glomerular filtration rate is reduced, it is not reduced as much as the renal blood flow; in other words, the filtration fraction remains relatively high.[19, 14] What mediates efferent arteriolar constriction is uncertain but it may possibly be renin, which is known to constrict the efferent arterioles,[20] liberated in response to the reduction in renal blood flow.

Now while the glomerular filtration rate is reduced, tubular reabsorption continues at its previous level and the net result is a retention of salt and water.[18] This retention leads to an increase in extracellular fluid volume including plasma volume. It should be reëmphasized that this retention of salt is believed to be due to the decreased glomerular filtration rather than to increased tubular reabsorption,[18, 19] which is in contrast with other mechanisms to be presently considered.

Raised Venous Pressure

At this point two vicious circles begin to operate. First, the rise in plasma volume produces an increase in venous pressure, and increased venous pressure, especially in the kidney,[21] but also elsewhere, is apparently a stimulus to increased tubular reabsorption of sodium. For it has been shown that temporary occlusion of the inferior vena cava *below* the renal veins,[22] or tourniquet occlusion of the leg veins,[23, 24, 25] or hepatic venous congestion,[26] or indeed congestion in any major peripheral venous bed,[27] leads to decreased sodium excretion. Second, when the venous pressure reaches significantly high levels, presumably the heart may eventually be "pushed over the hump" of Starling's curve so that the output actually falls. Such a fall leads to further impairment of renal blood flow, and so on.

At this stage another mechanism has been postulated by McMichael,[4] who suggests that a fall in cardiac output leads to inadequate blood flow to

[18] Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema, J. Clin. Invest. **25**: 389, 1946.

[19] Mokotoff, R., Ross, G., and Leiter, L.: Renal plasma flow and sodium reabsorption and excretion in congestive failure, J. Clin. Invest. **27**: 1, 1948.

[20] Merrill, A. J., Williams, J. R., and Harrison, T. R.: The site of action of the renal pressor substance, Am. J. M. Sc. **195**: 18, 1938.

[21] Blake, W. D., Wegria, R., Keating, R. P., and Ward, H. P.: Effect of increased renal venous pressure on renal function, Am. J. Physiol. **157**: 1, 1949.

[22] Farber, S. J., Becker, W. H., and Eichna, L. W.: Electrolyte and water excretions and renal hemodynamics during induced congestion of the superior and inferior venae cavae of man, J. Clin. Invest. **32**: 1145, 1953.

[23] Wilkins, R. W., et al.: Antidiuresis and renal vasoconstriction following venous congestion of the limbs in normal, hypertensive and splanchnicectomized subjects, J. Clin. Invest. **28**: 819, 1949.

[24] Fitzhugh, F. W., et al.: The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects, J. Clin. Invest. **32**: 1163, 1953.

[25] Judson, W. E., et al.: The hemodynamic and renal functional effects of venous congestion of the limbs in patients with diabetes insipidus, J. Clin. Invest. **29**: 826, 1950.

[26] Stamler, J., et al.: Relationship of elevated renal venous pressure to sodium clearances and edema formation in unanaesthetized dogs, Am. J. Physiol. **166**: 400, 1951.

[27] Frieden, J.: Effects of chronic peripheral venous congestion on renal sodium excretion, Am. J. Physiol. **168**: 650, 1952.

the venomotor center with resulting increase in venomotor tone and further rise in venous pressure.

Some of the experiments designed to explore the influence of increased venous pressure on the cycle described deserve to be considered in some detail. It has been shown that the generalized venous congestion produced by artificial pericardial effusion, without reducing blood pressure, cardiac output, renal blood flow or glomerular filtration rate, leads to decreased sodium and water excretion.[28] Similarly, the ligation of major veins severally in dogs, producing elevation of peripheral venous pressures, was paralleled by a fall in sodium excretion, though renal plasma flow and glomerular filtration rate remained unchanged.[27] These observations imply that tubular reabsorption was actively increased.

Further, in a spontaneous superior vena caval syndrome it was demonstrated that the proclivity to edema formation was not limited to the territory of increased venous pressure,[29] for, whereas facial edema was apparent on awakening in the early morning, marked edema of the feet occurred when the patient became ambulatory—the excess of extracellular fluid was mobile. The central rôle of the kidney in this syndrome was demonstrated by giving the patient an oral salt load, following which a marked impairment of urinary sodium excretion was observed.

It is important to realize that many of the experiments, designed to demonstrate the effects of increased venous pressure, have been acute experiments performed on animals and may well produce results which have no parallel in the chronic raised venous pressure of clinical heart failure. Indeed, when renal venous pressure was sustained experimentally by ligation of the inferior vena cava *above* the renal veins, early changes did not persist.[30] Renal blood flow, glomerular filtration rate and sodium excretion were at first reduced; but, within a week, these values were again approaching normal though the renal venous pressure remained elevated.

Hormones

It is widely believed that hormones are responsible for the retention of salt and water by the kidney in many edematous states. A simple and direct piece of evidence that sodium retention is encouraged by hormonal influence is the demonstration that its retention is not exclusively renal. For it has been shown in heart failure that not only the kidneys, but also the sweat glands,[2] salivary glands [31] and colon [32] eliminate less sodium than normally.

[28] Fishman, A. P., et al.: Mechanisms of edema formation in chronic experimental pericarditis with effusion, J. Clin. Invest. **29**: 521, 1950.

[29] Rice, L., et al.: A case of spontaneous thrombosis of the superior vena cava with some observations on the mechanism of edema formation, Am. Heart J. **43**: 821, 1952.

[30] Hwang, W., et al.: Effects of sustained elevation of renal venous pressure on sodium excretion in unanaesthetized dog, Am. J. Physiol. **162**: 649, 1950.

[31] White, A. G., Gordon, H., and Leiter, L.: Studies in edema. II. The effect of congestive heart failure on saliva electrolyte concentrations, J. Clin. Invest. **29**: 1445, 1950.

[32] Berger, E. Y., and Steele, J. M.: Suppression of sodium excretion by the colon in congestive heart failure and cirrhosis of the liver demonstrated by the use of cation exchange resins, J. Clin. Invest. **31**: 451, 1952.

It is also known that excretion of sodium in the sweat is reduced by the administration of desoxycorticosterone acetate or corticotropin.[33]

Equally provoking is the evidence of increased antidiuretic activity which has been demonstrated in the urine of patients with heart failure.[34, 35] Other investigators, however, have been unable to find significantly increased antidiuretic activity in the serum or plasma of such patients.[36, 37] Divergent findings and opinions have also characterized studies on corticoid excretion, some workers finding increased and others decreased amounts of corticoid substances in the urine. There is some evidence that the kidneys retain corticoid hormones in congestive failure.[38]

If we accept a forward failure hypothesis and agree that an inadequate cardiac output, by reducing renal blood flow, is the taproot of edema formation in heart failure, then it is possible also that a reduction in blood flow to other organs and areas may contribute to the over-all picture. A possible effect of impaired hepatic blood flow may well be the formation of the vasodepressor material (VDM) of Shorr by the relatively anoxic liver. VDM has been identified as ferritin[39] and has been shown to have antidiuretic effect.[40] This effect is mediated through the pituitary, for Shorr has shown that in animals from which the pituitary has been removed, VDM no longer exerts an antidiuretic action. Impairment of hepatic blood flow might lead not only to the liberation of VDM but also to impairment of its VDM-inactivation system.[41]

The normally functioning liver probably inactivates both the antidiuretic hormone of the posterior pituitary[42] and corticoids from the adrenal cortex.[43, 44] The relatively anoxic liver may be deficient in this respect, and so indirectly increase salt and water retention.

[33] Conn, J. W.: Electrolyte composition of sweat. Clinical implications as an index of adrenal cortical function, Arch. Int. Med. **83**: 416, 1949.

[34] Bercu, B. A., Rokaw, S. N. and Massie, E.: Antidiuretic action of the urine of patients in cardiac failure, Circulation **2**: 409, 1950.

[35] Dochios, M., and Dreifus, L. S.: Antidiuretic hormone studies in patients presenting edema, Am. J. M. Sc. **222**: 538, 1951.

[36] Perry, W. F., and Fyles, T. W.: Antidiuretic activity of the serum of normal and diseased subjects, J. Clin. Endocrin. and Metab. **13**: 64, 1953.

[37] Stein, M., Schwartz, R. and Mirsky, I. A.: The antidiuretic activity of plasma of patients with hepatic cirrhosis, congestive heart failure, hypertension and other clinical disorders, J. Clin. Invest. **33**: 77, 1954.

[38] Lasche, E., Perloff, W. H., and Durant, T. M.: Some aspects of adrenocortical function in cardiac decompensation, Am. J. M. Sc. **222**: 459, 1951.

[39] Mazur, A., and Shorr, E.: Hepatorenal factors in circulatory homeostasis. IX. The identification of the hepatic vasodepressor substance, VDM, with ferritin, J. Biol. Chem. **176**: 771, 1948.

[40] Baez, S., Mazur, A., and Shorr, E.: Hepatorenal factors in circulatory homeostasis. XX. Antidiuretic action of liver VDM concentrates, Fed. Proc. **7**: 5, 1948.

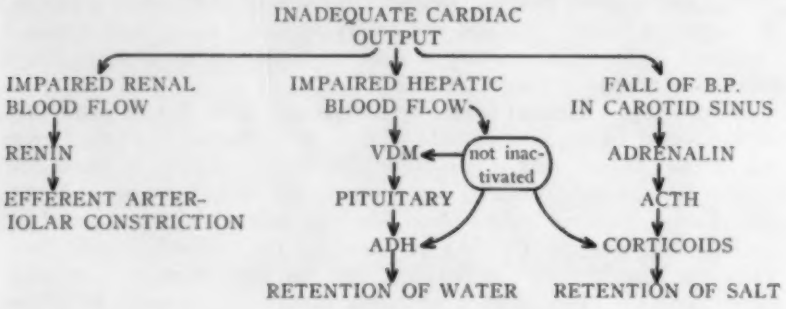
[41] Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S.: Hepatorenal factors in circulatory homeostasis. IV. Tissue origins of the vasotropic principles, VEM and VDM, which appear during the evolution of hemorrhagic and tourniquet shock, Circulation **3**: 42, 1951.

[42] Birnie, J. H.: The inactivation of posterior pituitary antidiuretic hormone by liver extracts, Endocrinology **52**: 33, 1953.

[43] Schneider, J. J., and Horstman, P. M.: Effects of incubating desoxycorticosterone with various rat tissues, J. Biol. Chem. **191**: 327, 1951.

[44] Louchart, J., and Jailer, J. W.: Inactivation of 11-dehydro-17-hydrocorticosterone by tissue slices, Proc. Soc. Exper. Biol. and Med. **79**: 393, 1952.

Possible mechanisms of excess corticoid production (if such occurs) may be the "stress" of heart failure, or, again, the inadequate cardiac output may lead to a fall in blood pressure in the carotid sinus with resulting liberation of adrenalin [45] which in turn stimulates the pituitary to put out corticotropin.[46] These various hormonal hypotheses may be linked together diagrammatically as follows:



Mechanical Factors

Little enough is known of the effects of simple mechanical factors, such as posture and exercise, on renal performance in health and in heart disease. Merrill and Cargill [47] have shown that exercise in cardiac patients reduces their renal plasma flow. Newman [48] by simple clinical tests on patients with congestive failure showed that the mildest of exertion (standing and walking) produced a selective pronounced decline in sodium chloride excretion with less marked water retention. In the normal subject standing caused less retention of salt but a more striking retention of water. To demonstrate that the retention of water and of salt were independent, antidiuresis in the normal subject was inhibited by a dose of alcohol before standing; as expected the water retention was largely prevented but salt retention was unaffected. Then again, by bandaging the legs before the subject stood, it was demonstrated that the sodium retention could be largely abolished, while antidiuresis was relatively unaffected.

Other investigators [49] have demonstrated that compression of the legs in healthy sitting males causes a well marked increase in urinary sodium output. No consistent effect was observed with the subjects recumbent.

[45] Kaindl, F., and von Euler, U. S.: Liberation of nor-adrenaline and adrenaline from the suprarenals of the cat during carotid occlusion, Am. J. Physiol. **166**: 284, 1951.

[46] Farrell, G. L., and McCann, S. M.: Detectable amounts of adrenocorticotrophic hormone in blood following epinephrine, Endocrinology **50**: 274, 1952.

[47] Merrill, A. J., and Cargill, W. H.: The effect of exercise on the renal plasma flow and filtration of normal and cardiac subjects, J. Clin. Invest. **27**: 272, 1948.

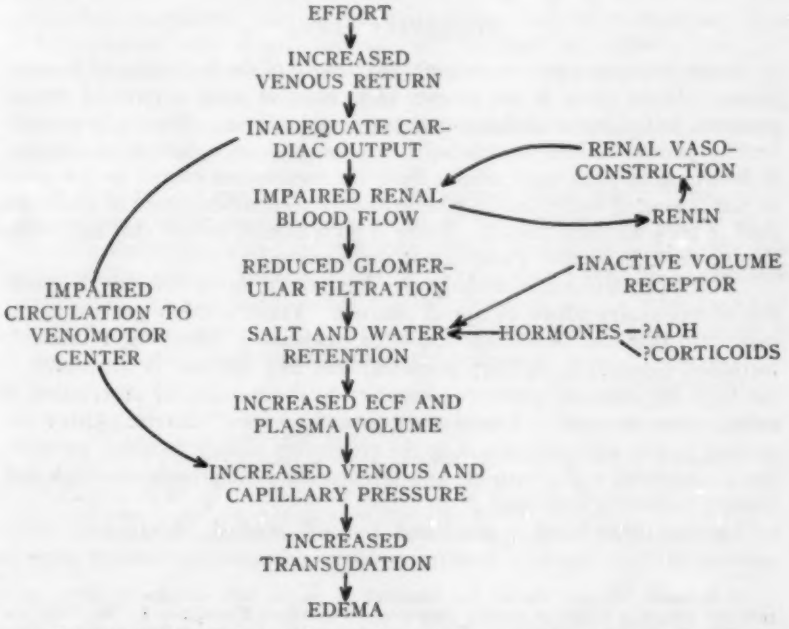
[48] Newman, E. V.: Metabolic adjustments to normal and disturbed circulation in man, New Eng. J. Med. **250**: 347, 1954.

[49] Lusk, J. S., Viar, W. N., and Harrison, T. R.: Further studies on the effect of changes in the distribution of extracellular fluid on sodium excretion. Observations following compression of the legs, Circulation **6**: 911, 1952.

Similarly, compression of the neck in normal sitting subjects caused increased output of sodium chloride, whereas little or no effect was observed if the subjects were lying down.[50] In patients with congestive failure, on the other hand, neck compression failed to cause significant increase in sodium excretion.[51]

Normal subjects excreted much less water and sodium when they were sitting than when they were lying. This inhibitory effect of sitting could be partly overcome by neck compression.[52] The influence of posture on the excretion of sodium and water was found to be markedly diminished in the presence of congestive failure.[53] These authors therefore postulate a "volume center" which, when intracranial pressure is lowered, stimulates the renal tubules to reabsorb more sodium, and they conclude that this volume receptor is inactive or overshadowed in congestive heart failure.

The main hypotheses so far discussed may now be summarized diagrammatically:



[50] Viar, W. N., et al.: The effect of posture and of compression of the neck on excretion of electrolytes and glomerular filtration: further studies, Circulation **3**: 105, 1951.

[51] Lombardo, T. A., and Harrison, T. R.: Effect of neck compression on sodium excretion in subjects with congestive heart failure, Circulation **7**: 88, 1953.

[52] Lewis, J. M., Buie, R. M., Sevier, S. M., and Harrison, T. R.: The effect of posture and of congestion of the head on sodium excretion in normal subjects, Circulation **2**: 822, 1950.

[53] Lombardo, T. A.: The effect of posture on the excretion of water and sodium by patients with congestive heart failure, Circulation **7**: 91, 1953.

The acceptance of forward failure should not necessarily imply complete denial of backward failure. There is room for two or more varieties of failure and there is good reason to believe that they exist. At least it is certain that the sequence of events in all episodes of congestive heart failure is not identical. In the case described by Newman and Fischel [54] there were marked and clearcut—and unexpected—differences when congestive failure was precipitated in the same patient by two methods, first by administering salt, and then by withholding digitalis. When salt was administered there was a rise in venous pressure and gain in weight, but dyspnea was not induced. When digitalis was withheld, the venous pressure rose similarly but without a gain in weight and dyspnea was now prominent. Reichsman and Grant [55] had previously shown that the withdrawal of digitalis led to a rise in venous pressure before a gain in weight. Such a sequence as surely suggests the validity of backward failure as the findings of Warren and Stead [18] indicate forward failure.

Pulmonary Edema

Acute pulmonary edema certainly bears none of the hallmarks of forward failure. It can occur in the absence of increase in weight, elevated venous pressure, hemodilution and manifest peripheral edema. When a previously healthy patient suffers myocardial infarction and, in a matter of minutes, is drowning in pulmonary edema fluid, the mechanism cannot be the same as that operating in the patient who gradually accumulates liters of unwanted fluid in his peripheral tissues. There is no reason to believe that salt retention by the kidney plays a rôle in this acute drama.

Much speculation and investigation has been directed towards the problem of pulmonary edema in mitral stenosis. There is fairly general agreement [56, 57] that the immediate cause of pulmonary edema is a critically increased pulmonary capillary pressure; and this increase is attributed to the high left auricular pressure secondary to the mechanical obstruction of mitral valve stenosis. This then is pure "backward" failure. Other important factors which contribute to the production of high capillary pressures are a competent right ventricle and the absence of a protectively high pulmonary arteriolar resistance.

On the other hand Araujo and Lukas [58] studied 34 cases of mitral stenosis of high degree. Resting capillary pulmonary pressures were in

[54] Newman, W., and Fischel, L.: Observations on the daily changes in venous pressure and weight in a case of chronic congestive heart failure, Circulation **1**: 706, 1950.

[55] Reichsman, F., and Grant, H.: Some observations on the pathogenesis of edema in cardiac failure, Am. Heart J. **32**: 438, 1946.

[56] Draper, A., et al.: Physiologic studies in mitral valvular disease, Circulation **3**: 531, 1951.

[57] Gorlin, R., et al.: Studies of the circulatory dynamics of mitral stenosis. II. Altered dynamics at rest, Am. Heart J. **41**: 30, 1951.

[58] Araujo, J., and Lukas, D. S.: Interrelationships among pulmonary "capillary" pressure, blood flow and valve size in mitral stenosis. The limited regulatory effects of the pulmonary vascular resistance, J. Clin. Invest. **31**: 1082, 1952.

the range of the colloid osmotic pressure of plasma, yet no pulmonary edema occurred in any of these cases. On exercise the pulmonary capillary pressure exceeded the colloid osmotic pressure, yet pulmonary edema occurred in only one patient. These authors conclude that pulmonary resistance is not the mechanism of protection and they attribute the failure to develop pulmonary edema rather to changes in permeability of the alveolar-capillary membrane—such as pericapillary fibrosis or thickening of capillary basement membrane.

Gorlin [59] concludes that the major determinants of pulmonary edema are increase in heart rate and increase in cardiac output. Ellis and coworkers [60] drew attention to the fact that the development of pulmonary edema required reasonably good cardiac function; all but one of their 11 cases had normal sinus rhythm and good cardiac outputs which could be increased with exercise. In a further study [61] these authors correlated postmortem findings with the clinical course of the disease and found that of the patients with pulmonary edema less than half (five of eleven) had severe stenosis. This is in agreement with Wood's impression [62] that patients suffering from pulmonary edema are not necessarily advanced cases of stenosis—rather to the contrary. In his series he found that it tended to occur in relatively young women who had average degrees of stenosis, and in whom pulmonary vascular resistance was unusually low.

It is clear that much remains to be learned about the mechanisms of edema formation in heart failure. One of the problems at present is to reconcile conflicting data and opinions. This review makes no pretense at being exhaustive. Without referring to more than a fraction of available publications, its aim is to gather together some of the loose threads—of which there are many—into a provisional pattern which may furnish a frame of reference for future reading on this subject.

H. J. L. MARRIOTT

[59] Gorlin, R., et al.: Factors regulating pulmonary "capillary" pressure in mitral stenosis, IV, Am. Heart J. **41**: 834, 1951.
[60] Ellis, L. B., et al.: Studies in mitral stenosis. I. A correlation of physiologic and clinical findings, Arch. Int. Med. **88**: 515, 1951.
[61] Graham, G. K., et al.: Studies in mitral stenosis. II. A correlation of post-mortem findings with the clinical course in 101 cases, Arch. Int. Med. **88**: 532, 1951.
[62] Wood, P.: An appreciation of mitral stenosis, Brit. Med. J. **1**: 1051 and 1113, 1954.

REVIEWS

Das Inselsystem des Pankreas. By HELMUT FERNER. 186 pages; 17.5 × 24.5 cm. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune and Stratton, Inc., New York. 1952. Price, Ganzl. DM 29.70.

This book covers the findings of the past fifteen years concerning the development, histology and pathology of the endocrine pancreas. Particular attention is given to subjects pertinent to diabetes mellitus. The developments of knowledge have been facilitated by new staining methods to which the author of the book has contributed a modification of a silver method for staining the A cells of the islets.

From the histological appearance, the endocrine pancreas seems to be functional in the second fetal month. This finding would coincide with the belief that insulin does not cross the placenta, but that the fetus supplies its own. The acinar tissue, of which the function is held largely in abeyance until after birth, is relatively undeveloped during gestation. Thus islet tissue makes up 30 per cent of the total pancreas in the embryo as compared to 2 to 3 per cent in the adult. The islet cells are distinguishable long before islet grouping has appeared. The ratio of A to B cells at different ages varies. The A cells producing the hyperglycemic factor, glucagon, are about 40 per cent of the total in the newborn, but only about 20 per cent in the adult. In the infant of the diabetic mother, the ratio of the insulin producing B cells is higher than normal.

Data are summarized showing that a rise in blood sugar amounting to 15 mg. per cent occurs through childhood from the second to the fifteenth year.

The current views on the histological findings in the islets in diabetes mellitus are presented. The phases of hydropic degeneration, hyaline degeneration and fibrosis of the islets are discussed. The relationship between detectable B cell defect and diabetes remains inconsistent, but the factors of A cell action and other causes of increased insulin requirement are considered to account for some of the discrepancy. Evidence concerning a possible alphacytotropic action of the pituitary is summarized.

G. E. G.

Influenza and Other Virus Infections of the Respiratory Tract. By C. H. STUART-HARRIS, M.D., F.R.C.P., Professor of Medicine, University of Sheffield, England. 235 pages; 14 × 22.5 cm. Williams and Wilkins Company, Baltimore. 1953. Price, $6.00.

In recent years considerable knowledge has accumulated concerning the nature of diseases of viral origin. Despite these strides, such viral diseases comprise a large portion of the infectious discases of man not yet susceptible to specific therapy. High on the list of frequency among the virus infections of man are those of the respiratory tract. Among these, some are bothersome but not serious in nature while a few are distressing in their present form but of more importance for their potential danger. Chief among the latter group is influenza. Although usually seen as a self limiting condition, the specter of the pandemic of 1918 is always in the background.

In the present monograph, the author has drawn from his large store of clinical and laboratory experience in order to promote a better understanding of the respiratory diseases of proved and suspected viral origin.

The book consists of 14 chapters dealing primarily with influenza but discusses other viral infections of the respiratory tract, as well. Among these are: primary atypical pneumonia, psittacosis and ornithosis, Q fever and the common cold. Influenza is especially well covered with good sections on epidemiology and an excellent chapter dealing with the laboratory diagnosis of influenza. Discussions of egg

inoculation technics, hemagglutination-inhibition tests, mouse neutralization and complement-fixation methods are also included.

Additional chapters of importance are those concerning the differential diagnosis of respiratory infections, an evaluation of influenza vaccine therapy and its rôle in prevention, and a short chapter on the therapy of influenza and its complications.

Illustrations are plentiful and include exemplary clinical charts, x-rays and pathologic reproductions. A small bibliography is appended to each chapter and a subject index included at the end of the book.

J. B. W.

An Atlas of Exfoliative Cytology. By GEORGE N. PAPANICOLAOU, M.D., Ph.D., Clinical Professor of Anatomy Emeritus, Cornell University Medical College. Pages not numbered; 26 × 29.5 cm. (loose-leaf, limp leather binding). Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass. 1954. Price, $18.00.

This loose-leaf volume is an outstanding publication. It provides detailed descriptions and illustrations of the enormous variety of cells desquamated from normal or neoplastic epithelial surfaces. It illustrates significant exfoliated cells in a uniform manner according to their origins and then types. Further, it discusses their diagnostic significance.

Of the nine chapters, one is introductory, one deals with technic, and one discusses the criteria of malignancy. Each of the other chapters is devoted to a specific body system, discussing non-malignant cytology and malignant cytology of each component organ and making frequent references to the illustrative plates.

Certainly, the value of this work lies in great part in the 36 beautiful colored plates, most of them from drawings and some of them from photographs of cells. Twelve of these plates are devoted to cells from the female genital system. Wherever possible, non-malignant cells and malignant cells from similar organs are grouped separately.

The index is excellent, referring not only to the brief text but to the plates as well. The bibliography contains a large number of references to clinical states and pathologic lesions along with those references of a strictly cytologic nature.

In summary, this atlas is of great value to the pathologist and the clinician interested in exfoliative cytology and to the cyto-technologist who works daily with the problems of technic and interpretation. It has become a highly respected, ready reference volume in our laboratory.

W. C. E.

Methods in Medical Research. Vol. 6. Editor-in-Chief: J. MURRAY STEELE. Governing Board: IRVINE H. PAGE, Chairman; RENÉ J. DUBOS, C. N. H. LONG, CARL F. SCHMIDT, EUGENE A. STEAD and DAVID L. THOMSON. 271 pages; 14 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1954. Price, $7.00.

This volume is concerned with human genetics, environmental studies, statistics and design of facilities for study of animal metabolism. In the section on environmental research, the discussion of measurement of basal metabolic rate emphasizes the inadequacy of the surface area standard and considers "lean body mass" as a possible standard. Another chapter of current clinical interest is that concerned with the measurement of quantity and composition of sweat. The section on statistics is of particular importance providing a survey of the most acceptable practices of planning and evaluating medical research. The chapters on clinical trial and clinical surveys present the pitfalls and requirements of these treacherous, but necessary,

methods. The section on metabolism cages provides a collection of useful ideas on various devices for management of animals of various types in metabolism experiments.

G. E. G.

Physiological Cardiology. Publication Number 184, American Lecture Series. By ARTHUR RUSKIN, M.D., F.A.C.P., Associate Professor of Internal Medicine, University of Texas—Medical Branch, Galveston, Texas; Edited by ROBERT F. PITTS, M.D., Ph.D., Professor of Physiology and Biophysics, Cornell University Medical College, New York, N. Y. 370 pages; 14.5 × 22.5 cm. Charles C Thomas, Springfield, Ill. 1953. Price, $8.00.

The author of this useful monograph attempts to bridge the gap between experimental physiological cardiology and clinical medicine. Emphasis is placed on fundamental recent advance under such chapter headings as Origin and Propagation of the Heart Beat, Congestive Heart Failure, Coronary Heart Disease, Hypertensive Cardiovascular Syndrome, The Heart in Nephritis, Valvular Heart Disease, and others. The author index and the subject index are well detailed and valuable.

There are included a great many advances which can be discussed only briefly in a text of this size. Many of the subjects of necessity are therefore presented with little elaboration. However, this remains a useful volume which should prove a worthwhile reference in the rapidly advancing field of cardiology.

L. S.

The Psychiatrist: His Training and Development. Report of the 1952 Conference on Psychiatric Education held at Cornell University, Ithaca, N. Y., June 19–25, 1952. Organized and conducted by the American Psychiatric Association and the Association of American Medical Colleges. Editorial Board: JOHN C. WHITEHORN, M.D., Chairman; FRANCIS J. BRACELAND, M.D., VERNON W. LIPPARD, M.D., and WILLIAM MALAMUD, M.D. Editorial Assistants: STELLA BLOCH HANAU and ROBERT L. ROBINSON. 214 pages; 14.5 × 22.5 cm. American Psychiatric Association, Washington, D. C. 1953. Price, $2.50.

This is an interesting, informative report on the training of the psychiatrist. It outlines in detail the material and the skills that the psychiatrist is expected to acquire before completion of his training. It covers the varied methods of teaching the art of psychiatry; the types of training available; and the methods of selecting a psychiatric resident.

The report, in the process of discussing the aforementioned subjects, stresses ideas that will be of special interest to the internist. Implicit in the report is a formulation of what the psychiatrist has to offer a patient referred by the internist. Also included is a chapter which covers the internists' approach to patients and offers suggestions as to how psychiatric knowledge might help the internist establish a satisfactory relationship with his patient. The idea is advanced that adequate psychiatric training be given in medical school to all physicians on a level equivalent to the training in surgery and medicine. There is a necessity for this training, as pointed out in the report, because only heart disease, of all the "physical illnesses," is on a par with mental illness as a disabling disease in terms of numbers of days lost from work or normal activities. It is hoped that adequate medical school training in psychiatry will also be helpful in enabling the internist to use the special skills offered by the psychiatrist.

H. W. N.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Arthritis and Rheumatism: The Diseases and Their Treatment. By CHARLES LEROY STEINBERG, M.D., Director of Arthritis Clinic and Senior Attending Physician in Medicine, Rochester General Hospital, with five contributors. 326 pages; 23.5 × 15.5 cm. 1954. Springer Publishing Company, Inc., New York. Price, $10.00.

Beyond the Germ Theory: The Roles of Deprivation and Stress in Health and Disease. IAGO GALDSTON, M.D., Editor. 182 pages; 22 × 14 cm. 1954. A New York Academy of Medicine Book, Published by Health Education Council, New York. Price, $4.00.

The Doctor Writes: An Anthology of the Unusual in Current Medical Literature. Edited by S. O. WAIFE, M.D., F.A.C.P. 175 pages; 22.5 × 15 cm. 1954. Grune & Stratton, New York. Price, $3.75.

Donovanosis (Granuloma Inguinale, Granuloma Venereum). World Health Organization Monograph Series No. 24. By R. V. RAJAM, M.S., F.R.C.P., Director, Venereal Diseases Department, Government General Hospital, Madras, etc.; and P. N. RANGIAH, M.D., Associate Professor of Venereal Diseases, Madras Medical College, Madras, etc. 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $1.50.

Einrichtung und Arbeitsweise einer Blutbank. By DR. MED. HABIL. W. HEIM and DR. MED. HABIL. P. DAHR. 328 pages; 21 × 15.5 cm. 1954. Georg Thieme Verlag, Stuttgart; agents in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, $7.85.

Endemic Goiter: The Adaptation of Man to Iodine Deficiency. Harvard University Monographs in Medicine and Public Health Number 12. By JOHN B. STANBURY, M.D., GORDON L. BROWNELL, Ph.D., DOUGLAS S. RIGGS, M.D., and HECTOR PERINETTI, M.D., JUAN ITOIZ, Ph.D., ENRIQUE B. DEL CASTILLO, M.D. 209 pages; 21.5 × 14.5 cm. 1954. Harvard University Press, Cambridge. Price, $4.00.

Expert Committee on Biological Standardization: Seventh Report. World Health Organization Technical Report Series No. 86. 24 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

First International Conference of National Committees on Vital and Health Statistics: Report. World Health Organization Technical Report Series No. 85. 28 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

First Report on the Geographical and Geological Distribution of Carcinoma in the Netherlands. Volume I. Foundation for the Study of Psycho-physics. By DR. J. C. DIEHL, Formerly Surgeon-General of the Royal Netherlands Army; and DR. S. W. TROMP, Geological Consultant to the United Nations T.A.A., etc.

120 pages (with maps); 29 × 20.5 cm. (paper-bound). 1953. Foundation for the Study of Psycho-physics, Leiden, Netherlands. Price, $2.10.

Fundamentals of Anesthesia, Prepared under the Editorial Direction of the Consultant Committee for Revision of Fundamentals of Anesthesia, a publication of the Council on Pharmacy and Chemistry of the American Medical Association. 3d Ed. 279 pages; 24 × 16 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $6.00.

Heart Disease and Industry, with Particular Reference to Workmen's Compensation Cases. By MEYER TEXON, M.D., New York City; Forewords by SAMUEL A. LEVINE, M.D., and HUBERT WINSTON SMITH, LL.B., M.D. 324 pages; 26 × 17.5 cm. 1954. Grune & Stratton, New York. Price, $7.50.

Der Herzanfall Differentialdiagnose und Therapie. Nauheimer Fortbildungs-Lehrgänge, Bd. 19. VEREINIGUNG DER BAD NAUHEIMER ÄRZTE. 129 pages; 24.5 × 17 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, kart. DM 13.–

Hormones in Health and Disease: A Symposium Presented at the Twenty-fifth Graduate Fortnight of the New York Academy of Medicine, October Sixth to Seventeenth, 1952. Edited by ROBERT L. CRAIG, M.D. 346 pages; 21.5 × 14.5 cm. 1954. The Macmillan Company, New York. Price, $6.00.

Hospital Service in the United States: The 1953 Census of Hospitals. Thirty-third Presentation of Hospital Statistics by the Council on Medical Education and Hospitals of the American Medical Association. Approved Schools for Medical Technologists, X-ray Technicians, Physical Therapists, Occupational Therapists, Medical Record Librarians and Medical Record Technicians. Hospitals Registered by the American Medical Association. 108 pages; 29 × 21.5 cm. (paper-bound). 1954. Reprinted from The Journal of the American Medical Association, Hospital Number, May 15, 1954, with Supplement.

Manual of Proctology. By EMIL GRANET, M.D., Lecturer, Graduate School, Columbia University, etc. 346 pages; 21 × 14.5 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, $7.50.

Manual of Urology. By ALEC W. BADENOCH, M.A., M.D., Ch.M. (Aberd.), F.R.C.S., Surgeon to St. Peter's Hospital for Stone and other Genito-Urinary Diseases, etc. 555 pages; 25.5 × 19 cm. 1954. Grune & Stratton, New York. Price, $15.75.

A Methodological, Psychiatric and Statistical Study of a Large Swedish Rural Population. (Acta Psychiatrica et Neurologica Scandinavica Supplementum 89.) By TAGE LARSSON and TORSTEN SJÖGREN. 250 pages; 24.5 × 16.5 cm. (paper-bound). 1954. Ejnar Munksgaard, Copenhagen. Price, 25 Swedish crowns.

Methodology of Planning an Integrated Health Programme for Rural Areas: Second Report of the Expert Committee on Public-Health Administration. World Health Organization Technical Report Series No. 83. 46 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, $0.25.

Myokardstoffwechsel und Herztherapie. By DR. MED. FRITZ PENDL. 248 pages; 24.5 × 17.5 cm. 1954. Georg Thieme Verlag, Stuttgart; available in the

U.S.A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 29.70.

Peripheral Circulation in Man: A Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and JESSIE S. FREEMAN, M.B., B.S., D.P.H., assisted by JOAN ETHERINGTON. 219 pages; 21 × 14 cm. 1954. Little, Brown and Company, Boston. Price, $6.00.

Physiology and Biochemistry of the Skin. By STEPHEN ROTHMAN, M.D., Professor of Dermatology, University of Chicago. 741 pages; 25 × 17.5 cm. 1954. The University of Chicago Press, Chicago. Price, $19.50.

Practical Fluid Therapy in Pediatrics. By FONTAINE S. HILL, M.D., Assistant Professor of Pediatrics, University of Tennessee College of Medicine, Memphis, etc. 275 pages; 24 × 16 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $6.00.

Regulationsprüfung des Kreislaufs. By DR. MED. FRITZ SCHELLONG; Bearbeitet von DR. MED. BERNHARD LÜDERITZ. 150 pages; 24 × 16.5 cm. (paper-bound). 1954. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 20.–, geb. DM 22.–

Smallpox Vaccination: A Survey of Recent Legislation. Reprinted from the International Digest of Health Legislation, 1954, 5: 221–262. 39 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 50 cents.

The Surgery of Pulmonary Tuberculosis. By JAMES H. FORSEE, A.B., B.S., M.D., F.A.C.S., F.A.C.P., Colonel, M.C., U. S. Army, etc. 208 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $6.50.

Thorakoskopische Eingriffe am Nervensystem. By DR. MED. E. KUX; mit einem geleitwort von PROF. DR. B. BREITNER. 130 pages; 24.5 × 17.5 cm. 1954. Georg Thieme Verlag, Stuttgart; agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 28.50.

Treponematoses: A World Problem. By T. GUTHE, M.D., M.P.H., Chief, Venereal Disease and Treponematoses Section, World Health Organization; and R. R. WILLCOX, M.D., Physician-in-charge, Venereal Disease Department, King Edward VII Hospital, Windsor, etc. 79 pages; 24 × 18 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 50 cents.

Ultrasonic and Ultrashort Waves in Medicine. By JOHANNA M. VAN WENT, M.D., Director, Institute for Physical Medicine and Rheumatism, Amsterdam; Introduction by KENNETH PHILLIPS, M.D., F.A.C.P., Director, Parkway Medical Clinic, and Dept. Physical Medicine Jackson Memorial Hospital, Miami, Florida. 384 pages; 23.5 × 15.5 cm. 1954. Elsevier Publishing Company, Houston. Price, $9.00.

Why We Became Doctors. Edited by NOAH D. FABRICANT, M.D. 182 pages; 22.5 × 14.5 cm. 1954. Grune & Stratton, New York. Price, $3.75.

The Antiseptic, Monthly Journal of Medicine & Surgery: Golden Jubilee, April, 1954. 548 pages; 24.5 × 17 cm. (paper-bound). Proprietor: U. KRISHNA RAU, M.B., B.S.; Editor: U. VASUDEVA RAU, M.B., B.S. Published on the fifteenth of every month. Price, Rs. 6/– Foreign 12 Sh.; Subn. Rs. 7/8 Foreign 15 Sh. Address: "Ramarau Buildings," 323–24 Thambu Chetty St., Post Box 166, Madras –1.

COLLEGE NEWS NOTES

New Life Members

It is a pleasure for the College to announce that the following Fellows have become Life Members since the publication of the last list in the May issue of this journal:

Dr. James M. Moss, Alexandria, Va.
Dr. Roy E. Kinsey, Peekskill, N. Y.
Dr. Melvin H. Stich, Brooklyn, N. Y.
Dr. George G. Reader, New York, N. Y.
Dr. Ira L. Rubin, New York, N. Y.
Dr. Charles P. Archambeault, Washington, D. C.
Dr. Phillip Thomas Knies, Columbus, Ohio
Dr. Herbert Koteen, Pleasantville, N. Y.
Dr. Kelso Adair Carroll, Washington, D. C.

Gifts to College Library of Publications by Members

The College is indeed grateful to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

Herman N. Bundesen, M.D., F.A.C.P., Chicago—*Progress in the Prevention of Needless Neonatal Deaths*, with Edith L. Potter, M.D., William I. Fishbein, M.D., Frank C. Bauer, A.B., and Gertrude V. Plotzke, R.N.

Nathaniel E. Reich, M.D., F.A.C.P., Brooklyn—*The Uncommon Heart Diseases*

L. Minor Blackford, M.D., F.A.C.P., Atlanta, Ga.—*Mine Eyes Have Seen the Glory*

Mitchell A. Spellberg, M.D., F.A.C.P., Chicago—*Diseases of the Liver*

Bernard J. Alpers, M.D., F.A.C.P., Philadelphia—*Clinical Neurology* (3rd Edition)

Meyer Texon, M.D., F.A.C.P., New York City—*Heart Disease and Industry*

Jackson A. Smith, M.D. (Associate), Houston, Tex.—*Alcoholism*

Arthur Grishman, M.D., F.A.C.P., New York City—*Spatial Vectorcardiography*, with Leonard Scherlis, M.D.

Edward J. Stieglitz, M.D., F.A.C.P., Washington, D. C.—*Geriatric Medicine—Medical Care of Later Maturity* (3rd Edition)

This Library is maintained at College Headquarters and members frequently present copies of their books to the College; thus the Library has become a living memorial to the member-authors.

Coming A.C.P. Regional Meetings

WEST VIRGINIA, White Sulphur Springs, August 19, 1954; Paul H. Revercomb, M.D., Governor; Cyrus C. Sturgis, M.D., President of the College, Special Guest.

NORTH DAKOTA, Bismarck, September 11, 1954; Robert B. Radl, M.D., Governor; Cyrus C. Sturgis, M.D., President of the College, Special Guest.

MONTANA–WYOMING, September 15, 1954; Harold W. Gregg, M.D., Governor.

ARKANSAS–OKLAHOMA, Oklahoma City, October 8–9, 1954; A. A. Blair, M.D., and Wann Langston, M.D., respective Governors; M. A. Blankenhorn, M.D., Regent of the College, Special Guest. This Regional Meeting will be held in

conjunction with A.C.P. Postgraduate Course No. 1, "Selected Problems in Internal Medicine," under the direction of Dr. Langston.

MIDWEST (Indiana, Illinois, Iowa, Minnesota and Wisconsin), Indianapolis, October 9, 1954; James O. Ritchey, M.D., Howard Wakefield, M.D. (N. ILL.), Charles H. Drenckhahn, M.D. (S. ILL.), Willis M. Fowler, M.D., Wesley W. Spink, M.D., and F. W. Madison, M.D., respective Governors; Wendell A. Shullenberger, M.D., Chairman, Indianapolis.

SOUTHEASTERN (Alabama, Florida, Georgia, South Carolina, Cuba, Mississippi and Louisiana), Edgewater Park, Miss.; D. O. Wright, M.D., William C. Blake, M.D., Carter Smith, M.D., Robert Wilson, M.D., J. J. Centurion, M.D., L. J. Clark, Sr., M.D., and Marion D. Hargrove, M.D., respective Governors; D.O. Wright, M.D., General Chairman; Howard Holley, M.D., Birmingham, Program Chairman; William J. Atkinson, M.D., Mobile, Arrangements Chairman; William D. Stroud, M.D., Treasurer of the College, Philadelphia, Special Guest.

NEW MEXICO, Albuquerque, October 20, 1954; Walter I. Werner, M.D., Governor; Philip S. Hench, M.D., Regent of the College, Special Guest.

NEW ENGLAND (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont), Hartford, Conn., October 22, 1954; John Leonard, M.D. (General Chairman), Richard S. Hawkes, M.D., Richard P. Stetson, M.D., S. M. Gundersen, M.D., Marshall N. Fulton, M.D., and E. L. Amidon, M.D., respective Governors; Cyrus C. Sturgis, M.D., President of the College, and Edward R. Loveland, Executive Secretary of the College, Special Guests.

WESTERN PENNSYLVANIA, Pittsburgh, October 27, 1954; C. Howard Marcy, M.D., Governor; R. R. Snowden, M.D., Chairman. This Regional Meeting will be held in conjunction with A.C.P. Postgraduate Course No. 5, "Selected Subjects in Internal Medicine," under the direction of Dr. Snowden.

NEW JERSEY, Newark, November 3, 1954; Edward C. Klein, Jr., M.D., Governor; Cyrus C. Sturgis, M.D., President of the College, Special Guest.

WESTERN NEW YORK, Syracuse, November 19, 1954; Edward C. Reifenstein, M.D., Governor; Cyrus C. Sturgis, M.D., President of the College, and Edward R. Loveland, Executive Secretary of the College, Special Guests.

MICHIGAN, Grand Rapids, December 4, 1954; H. Marvin Pollard, M.D., Governor; Cyrus C. Sturgis, M.D., President of the College, Special Guest.

Several other Regional Meetings are in course of organization, including SOUTHERN ILLINOIS at Peoria during March, 1955; KANSAS at Wichita, March 18, 1955; and VIRGINIA at Richmond, February 24, 1955.

A.C.P. Committee on Military Affairs

President Cyrus C. Sturgis of the College has reactivated the Committee on Military Affairs of the College, with Dr. Richard A. Kern, Philadelphia, Chairman, Dr. John Minor, Washington, Dr. Maurice C. Pincoffs, Baltimore, and Dr. Irving S. Wright, New York, members. To this Committee will be referred all matters concerning military affairs that are referred to the College, one of which is the present study of military and civilian medical planning in time of war.

Change in Dates, A.C.P. Course No. 8

The American College of Physicians Postgraduate Course No. 8, "Gastroenterology," has recently been rescheduled and will be given Nov. 8–12, 1954, and not Nov. 15–19 as originally scheduled. Under the Directorship of Dr. Henry L. Bockus, F.A.C.P., the course will be held at the College of Physicians of Philadelphia

Building, under the auspices of the University of Pennsylvania Graduate School of Medicine.

A complete schedule of the A.C.P. Postgraduate Courses to be given this autumn will be found in the advertising section.

A.C.P. Research Fellowships and Traveling Scholarships

Applications for A.C.P. Research Fellowships must be submitted in duplicate to the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa., not later than Oct. 1, 1954. These Fellowships, designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation, will be available from July 1, 1955–June 30, 1956. The stipends are from $3,000–$3,500.

Letters of application for the A. Blaine Brower Traveling Scholarships and the Elizabeth Archbold Bowes Traveling Scholarship, which are administered by the College, are due in the Executive Offices of the College not later than Oct. 15. The two Brower Scholarships, of approximately $400 each, are awarded to "deserving and promising young physicians, preferably Associates of the College, for attendance for a short period of time for observation and study at an outstanding institution of medical teaching, research or practice." Similar rules govern the Bowes Scholarship, which is restricted to Canadian candidates.

Forthcoming Annual Sessions of the American College of Physicians

1955—April 25–29, Philadelphia, Pa.
1956—April 16–20, Los Angeles, Calif.

The American College of Physicians announces its Convention dates two years in advance in the hope that other medical societies, particularly state medical societies and others concerned with the field of Internal Medicine and its allied specialties, shall avoid conflicts for mutual benefit.

Meetings, A.C.P. Committee on Credentials

The Committee on Credentials of the American College of Physicians will meet in Philadelphia on Nov. 12–13, 1954. Proposals for action at that meeting must be received at College Headquarters not later than Sept. 14, 1954, in accordance with the By-Laws. The College Governors may require that proposals reach their offices for endorsement not later than Aug. 14, 1954. Additional meetings of the Committee will be held in Philadelphia, March 19–20, and April 23, 1955.

The James Alexander Miller Fellowship
for
Research in Tuberculosis and Allied Problems

The New York Tuberculosis and Health Association announces that a fellowship will be available from July 1, 1955, to June 30, 1956. Dr. James Alexander Miller was a Master of the American College of Physicians and served as President, 1935–36.

The Miller Fellowship is designed to support a qualified investigator in medical or biological sciences who will devote full time to a research project in tuberculosis or

allied problems. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice; and that he will be provided with the facilities necessary for the pursuit of the work.

The annual stipend will be $5,000.00. Consideration will be given for renewal of the Fellowship for one or more years.

Applications should be submitted in duplicate by Nov. 1, 1954. Application forms will be supplied on request. Address—The New York Tuberculosis and Health Association, 386 Fourth Ave., New York 16, N. Y. Awards will be announced Dec. 15, 1954.

Applications for Research Awards Accepted by A.H.A.

Applications for research awards to be made during the coming year by the American Heart Association and its affiliates throughout the country are now being accepted, it has recently been announced by Dr. Robert L. King, F.A.C.P., Seattle, Wash., Chairman of the Association's Scientific Council.

Applications for Research Fellowships and Established Investigatorships may be filed up to Sept. 15, 1954. Applications for research Grants-in-Aid will be accepted up to Dec. 1, 1954. Information and forms may be obtained from the Medical Director, American Heart Association, 44 E. 23rd St., New York 10, N. Y.

The research awards will be available for studies to be conducted during the year beginning July 1, 1955. Funds to support the research program are provided by the 1954 Heart Fund campaign conducted by the American Heart Association and its affiliated associations and chapters.

Established Investigatorships, awarded for one- to five-year periods subject to annual review, range from $6,000 to $9,000. They are available to scientists of proven ability who are engaged in a research career. Research Fellowships, awarded for one- or two-year periods, range from $3,500 to $5,500 and enable younger scientists to train for research careers under experienced supervision. Grants-in-Aid are awarded in varying amounts, usually not exceeding $10,000, for periods of one to three years, to experienced scientists working in non-profit institutions on specified programs of research.

Life Insurance Medical Research Fund
Research Fellowships and Grants

Applications for awards available July 1, 1955, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 29, 1954. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend $3,500, with allowances for dependents and necessary travel. (2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1954. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

Postgraduate Course in Practical Electrocardiology

A course in practical electrocardiology will be presented during the week of Dec. 6–10, 1954, under the auspices of the University of Texas Postgraduate School

of Medicine, Baylor University College of Medicine and the Houston Heart Association. The guest lecturer, Dr. Demetrio Sodi-Pallares, F.A.C.P., Chief of the Department of Electrocardiology of the National Institute of Cardiology of Mexico City, will lecture each evening during the week from Monday to Friday from 7:30 P.M. to 10:00 P.M. During daytime hours, registrants may attend various hospitals in the Medical Center when routine tracings are being read and, in addition, will receive individualized instruction in the interpretation of specific tracings by various members of the faculties of the two schools. Further details may be obtained from the University of Texas Postgraduate School of Medicine or from Earl F. Beard, M.D., Kelsey & Leary Clinic, 311 Hermann Professional Bldg., Texas Medical Center, Houston 25, Tex.

The New York Academy of Medicine will hold its Twenty-Seventh Annual Graduate Fortnight on Infections and Their Management, October 18–29, 1954. The program will consist of 20 evening lectures, 6 morning panel meetings, 10 hospital clinics and a scientific exhibit. Fees for Non-Fellows of the Academy: $10.00 for the entire program, $5.00 for either first or second week.

Program and registration card may be obtained from Robert L. Craig, M.D., Executive Secretary, Committee on Medical Education.

Forthcoming Meetings in Other Countries

Meeting Dates and Locations	*Details*
Great Britain	
Sept. 1–8, Oxford British Association for the Advancement of Science—Annual Meeting	The Association, Burlington House, Piccadilly, London, W.1.
Sept. 8–9, Oxford Physiological Society (Meeting open to members; any guests should be introduced by members)	Dr. W. D. M. Paton, University College Hospital Medical School, London, W.C.1.
Sept. 9–12, Harrogate Chartered Society of Physiotherapists Annual Congress	Philip Gaunt, M.C.S.P., The Private Clinic, 38, Park Square, Leeds.
Sept. 14–15, Reading Society for General Microbiology	Dr. E. F. Gale, Biochemical Laboratory, The University, Cambridge.
Oct. 9, London British Dietetic Association General Meeting	British Dietetic Association, 251, Brompton Road, London, S.W.3.

Meeting Dates and Locations	*Details*
Oct. 15–16, London Biochemical Society	Prof. F. L. Warren, Dept. of Biochemistry, London Hospital Medical School, London, E.1.
Nov. 5–6, London British Society of Gastroenterology Annual Meeting (Open to members; guests should be introduced by members)	Mr. Hermon Taylor, F.R.C.S., 14, Upper Harley St., London, W.1.
Nov. 15–19, London London Medical Exhibition At Royal Agricultural Hall, London, S.W.1	London Medical Exhibition, 194–200, Bishopsgate, London, E.C.1.
Austria	
Sept. 20–22, Innsbruck Austrian Society for Microbiology and Hygiene	Die Tagungssekretariats, Institut für biochem. Technologie und Lebensmittelchemie, Schlögelgasse, 9, Graz.
Brazil	
Dec. 1–7, Sao Paulo First International Congress on Medicinal and Similar Plants	Prof. Dr. Paulo de Toledo-Artigas, rua Tres Rios 363, Sao Paulo.
Dec. 1–8, Sao Paulo Third Pan American Pharmaceutical and Biochemical Congress	Pr. Carlos H. Liberalli, rua Tres Rios 363, Sao Paulo.
Canada	
Sept. 11, Montreal International Organization against Trachoma General Assembly	Prof. Arnold Sorsby, 45, Lincoln's Inn Fields, London, W.C.2.
Chile	
October, Santiago Fourteenth Pan American Sanitary Conference	Dr. M. E. Bustamente, Pan American Sanitary Bureau, Washington 6, D. C.
France	
Sept. 6–12, Paris Fifth International Congress of the International Society of Haematology	Secretary of the Congress, Expansion Scientifique, 15, rue Saint-Benoit, Paris 6.

Meeting Dates and Locations	*Details*
Sept. 13–19, Paris Fifth International Congress of Blood Transfusion	Colonel Julliard, 57, boulevard d'Auteuil, Boulogne sur Seine.
Oct. 15–17, Marseille Fifth International Colloquium on Dermatology and Syphilography	Dr. J. Bonnet, Clinique dermatologique, Hôtel-Dieu, Place Daviel, Marseille.
Germany	
Nov. 18–20, Dusseldorf Congress of Industrial Medical Officers	Deutsche Gesellschaft für Arbeitsschutz e.V., Mainzer Lanstrasse, 178, Frankfurt-am-Main.
Italy	
Sept. 6–10, Rome Third International Poliomyelitis Congress	Secretariat, Third International Poliomyelitis Congress, Via Lucullo, 6, Rome.
Sept. 13–19, Naples Eleventh International Congress of Industrial Medicine	Dr. P. S. Pringle, British Electricity House, Trafalgar Buildings, London, S.W.1.
Sept. 13–20, Rome and Salerno Fourteenth International Congress of the History of Medicine	Dr. M. Galeazzi, Instituto di Storia della Medicina, Citta Universitaria, Rome.
Sept. 15–21, Gardone Medical Women's International Association 8th Congress	Dr. Janet Aitken, 30a, Acacia Road, London, N.W.8.
Sept. 23–25, Rome Fourth International Therapeutic Congress	Prof. Luigi Travia, Clinica Medica-Policlinico, Rome.
Sept. 26–Oct. 2, Rome Eighth General Assembly of the World Medical Association	Dr. L. H. Bauer, F.A.C.P. World Medical Association, 345 East 46th St., New York 17.

Meeting Dates and Locations	*Details*
Netherlands	
Sept. 14–18, Amsterdam Third Congress of the International Union of Nutritional Sciences	Dr. G. H. Bourne, London Hospital Medical School, Turner Street, London, E.1.
Spain	
Sept. 26–Oct. 2, Madrid Thirteenth Conference of the International Union against Tuberculosis	Secretariat, Escuela de Tisiologia, Ciudad Universitaria, Madrid.
Oct. 4–8, Barcelona Third International Congress on Diseases of the Chest	Dr. A. Caralps, Third International Congress, Corcega, 393, Barcelona.
Sweden	
Sept. 15–18, Stockholm Third International Congress of Internal Medicine	The Secretary General, Prof. Anders Kristenson, Karolinska sjukhuset, Stockholm, 60.

Army Medical Education Committee Formed

A new committee on Army Medical Education has recently been formed by the National Academy of Sciences, National Research Council, at the request of the Army Medical Service.

The Committee, which held its organizational meeting on June 5, replaces the former Advisory Committee of the Army Medical Service Graduate School, Walter Reed Army Medical Center. This newly organized committee, instead of being limited to the scope of operations of the School, will deal with professional education and training problems of the Army Medical Service in its entirety and will act in an advisory capacity to the Surgeon General.

Membership of the Committee on Army Medical Education includes: Dr. Dean A. Clark, General Director, Massachusetts General Hospital, Chairman; Dr. Joseph M. Hayman, Jr., F.A.C.P., Dean, Tufts College Medical School; Dr. Franklin C. McLean, University of Chicago; Dr. John H. Mulholland, Department of Surgery, New York University; Dr. I. S. Ravdin, Department of Surgery, University of Pennsylvania; Dr. Grant Taylor, Graduate School of Medicine, University of Texas; Dr. Gaylord W. Anderson, University of Minnesota; and Dr. Tom Bradley, Executive Secretary of the National Research Council.

Clinical Fellowships in the Management of Poliomyelitis

One-year clinical fellowships in the management of poliomyelitis are being offered for the first time by the National Foundation for Infantile Paralysis as part of its continuing program of professional education.

The purpose of these fellowships is to train physicians in the various aspects of the total care of the poliomyelitis patient.

Applicants for fellowships must be U. S. citizens (or applicants for citizenship), and must have completed at least one year of internship in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association.

Selection of candidates will be made on a competitive basis by the National Foundation's Clinical Fellowship Committee. Stipends will range from $300 to $400 a month depending upon marital status and number of dependents. Before applying for a fellowship, the candidate should arrange for a program of full-time study at any institution having suitable facilities for this type of training.

Applications for fellowships received by Sept. 1 will be considered in November; those received by Dec. 1 will be considered in February; those submitted by March 1 will be considered in May.

For application forms and further information, address the National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5, N. Y.

Dr. George Morris Piersol Elected Dean of the University of Pennsylvania Graduate School of Medicine

Dr. George Morris Piersol, M.A.C.P., on June 30, 1954, relinquished his work as Professor of Medicine and Director, Center for Instruction and Research in Physical Medicine, University of Pennsylvania Graduate School of Medicine, and as Professor of Physical Medicine of the University of Pennsylvania School of Medicine and as Director of the Departments of Physical Medicine and Rehabilitation of the Hospital of the University of Pennsylvania, and has been appointed Dean of the University of Pennsylvania Graduate School of Medicine, to succeed Dr. Aims C. McGuinness, who has resigned.

No more fitting appointment could be made, for Dr. Piersol is steeped in the history and traditions of the Graduate School of Medicine, having been an original faculty member, for many years Chairman of the Department of Internal Medicine and more recently Professor of Medicine and Director of the Center for Instruction and Research in Physical Medicine. The late Dr. George Meeker was the organizing genius of a new type of Graduate School of Medicine, and with such men as Dr. Piersol, as Vice Dean of Medicine, laid the unique and effective foundations, bringing together into one institution the former Medico-Chirurgical College of Philadelphia, the Polyclinic Medical School and the University of Pennsylvania. Dr. Meeker retired in 1941, was succeeded by Dr. Robin Buerki, F.A.C.P., who in 1948 became Vice President of the University in charge of Medical Affairs. Dr. Buerki was succeeded by Dr. William Parker (1948–50), who in turn was succeeded by Dr. Aims C. McGuinness (1951–54).

Dr. Piersol's services to his Alma Mater, the University of Pennsylvania, scarcely transcend his services to the American College of Physicians. He became a Fellow in 1922, served as the Secretary-General for twenty-five years and as Chairman of the Committee on Credentials, the most important Committee of the College, for even a longer time, and still occupies that post. He was President for 1933–34. A Mastership was conferred upon him in 1947, and the Alfred Stengel Memorial Award was conferred on him in 1951.

Committee on Medical Educational Films Appointed by the A. C. P.

In accordance with directions of the Board of Regents, Dr. Cyrus C. Sturgis, President of the College, has appointed a Committee on Medical Educational Films, as follows, for the purpose of passing upon new films as they are in production and

in which the College is interested, regardless of the producer, the Committee to function only on request:

Wallace M. Yater, M.D., Washington, D. C.
T. Grier Miller, M.D., Philadelphia, Pa.
George Morris Piersol, M.D., Philadelphia, Pa.

The Committee at its discretion may appoint or select two or more men who are qualified in special fields and subjects to pass upon the scenario, the parts as the film develops and then the final film as a whole.

Omaha Mid-West Clinical Society

The Twenty-Second Annual Assembly of the Omaha Mid-West Clinical Society will be held at the Paxton Hotel, Omaha, Nebr., October 25–28, inclusive, 1954. Dr. Friedrich W. Niehaus, a Life Fellow of the American College of Physicians, is the President-Elect.

Dr. Cyrus C. Sturgis, F.A.C.P., President of the College, received the honorary degree of LL.D. at the commencement of the University of Puerto Rico on June 1, 1954. Dean E. Harold Hinman presented Dr. Sturgis and read his citation. This was the first graduation of a full four-year medical class at the University of Puerto Rico. There were 45 graduates.

Dr. Sturgis represented the American College of Physicians and the American Medical Association at the Annual Meeting of the Canadian Medical Association at Vancouver, B. C., June 16–18, and presented a paper on the scientific program.

Dr. Sturgis also was the speaker at the Annual Meeting of the Canadian Heart Association at Vancouver, B. C., on June 15, 1954.

Dr. Edward C. Reifenstein, Sr., F.A.C.P., Syracuse, College Governor for Western New York, received one of the George Arents Pioneer Medals from Syracuse University on June 5. The awards, established in 1939, are made annually to not more than three outstanding alumni of Syracuse University. A graduate of Syracuse University College of Medicine in 1904, Dr. Reifenstein taught there from that year until he became Emeritus Professor of Medicine in 1946. Always interested in the affairs of his alma mater, Dr. Reifenstein is a member of the Syracuse University Board of Trustees. He has been a Fellow of the College since 1921.

Dr. Frank P. Pignataro, F.A.C.P., Red Bank, was recently elected President of the New Jersey Neuropsychiatric Association.

Newly elected officers of the Texas Academy of Internal Medicine include Dr. Martin S. Buehler, F.A.C.P., Dallas, President; Dr. Robert A. Hettig (Associate), Houston, Vice President; and Dr. George M. Jones, F.A.C.P., Dallas, Treasurer.

Dr. Thomas F. Keliher, F.A.C.P., Washington, D. C., Clinical Associate Professor of Medicine at Georgetown University School of Medicine, received the Bene Merenti Medal at the annual commencement of Georgetown University on June 7. The award is made annually in recognition of outstanding service to the University.

Rear Adm. Bartholomew W. Hogan, (MC), USN, F.A.C.P., received the degree of Doctor of Laws (honoris causa) from Villanova University on June 7. On April 30, Adm. Hogan was appointed Deputy and Assistant Chief of the Bureau of Medicine and Surgery, succeeding Vice Adm. Clarence J. Brown, who retired May 1.

Dr. Louis F. Bishop, F.A.C.P., New York City, was recently elected President of the New York Cardiology Society.

Dr. Carlisle Morse, F.A.C.P., Louisville, has been appointed Governor for Kentucky and Vice Chairman of the Committee on Detection and Education of the American Diabetes Association.

Drs. Leon H. Collins, Jr., F.A.C.P., Philadelphia, and Archibald C. Cohen, F.A.C.P., Butler, were elected President and President-Elect, respectively, of the Pennsylvania Trudeau Society at its meeting in Harrisburg on April 14.

Dr. Noble P. Sherwood, F.A.C.P., Emeritus Professor of Bacteriology at the University of Kansas, will present a paper on "Pioneers and Pioneering in Bacteriology and Immunity in the United States from 1877 to 1907" before the International Congress in Rome and Salerno, Italy, September 11–21, 1954. Dr. Sherwood will make a rather extensive trip to England, Scotland and the Continent to gather information to be used in his lectures on the history of bacteriology and immunity at the University of Kansas School of Medicine.

Thirty-six doctors from six foreign countries and thirteen States attended the Fortieth Annual Session of the Trudeau School of Tuberculosis, which ended its four-week course on June 25. Sessions of the School were held at Trudeau Sanatorium and other divisions of the Trudeau-Saranac Institute, as well as at neighboring sanatoria and hospitals.

The faculty was composed of physicians, surgeons, and scientists from the Saranac Lake area as well as several guest lecturers. Among the latter were the following Fellows of the College: Dr. Richard V. Ebert, Park Ridge, Ill.; Dr. Theodore E. Woodward, Baltimore; Dr. Anthony J. Lanza, New York City; Dr. Oscar A. Sander, Milwaukee; and Dr. David T. Smith, Durham, N. C.

Speaking on "A New Look at the Old Ticker," Dr. Theodore G. Klumpp, F.A.C.P., New York City, President of Winthrop-Stearns Inc., delivered the banquet address at the Fifth Annual Postgraduate Session of the Barbour-Randolph-Tucker Medical Society, which was held at the Tygart Valley Country Club near Elkins (W. Va.), June 17.

Dr. Henry A. Monat, F.A.C.P., Washington, D.C., delivered a paper entitled "Nutrition of Aged Cardiacs" at the Third International Gerontological Congress in London, England, July 20.

In addition to the speakers reported in last month's issue of this journal, Dr. Louis F. Bishop, F.A.C.P., New York City, spoke on "The Prognosis of the Paroxysmal Tachycardias" at the Third Annual Convention of the American College of Cardiology, held in Chicago in May.

Dr. Mavis P. Kelsey, F.A.C.P., Houston, Tex., recently completed a six weeks' trip to England, Switzerland, Holland, Germany, and France. He addressed the Postgraduate School of Medicine in London on June 10 on "Cancer of the Thyroid."

Dr. Chester S. Keefer, F.A.C.P., Boston, will participate in the opening discussion of "Social Aspects of Poliomyelitis" at the Third International Poliomyelitis Conference, to be held Sept. 6–10 in Rome, Italy. The concluding paper, "Future Prospects," will be delivered by Dr. John R. Paul, F.A.C.P., New Haven, Conn.

Drs. Charles C. Wolferth, F.A.C.P., and William A. Jeffers, F.A.C.P., Philadelphia, were among those who reported on "Experiences with Thoracolumbar Sympathectomy and with Combined Adrenalectomy-Sympathectomy in the Treatment of Patients with Essential Hypertension" at the annual meeting of the Society for Vascular Surgery, which was held in San Francisco on June 20.

At the annual session of the American Gastroscopic Society, held in San Francisco, June 20, Dr. Rudolf Schindler, F.A.C.P., Los Angeles, spoke on "The Story of the Building of the Flexible Gastroscope" at the annual banquet. In addition, Dr. Schindler gave a presentation entitled "Gastroscopic Observations in Post-Operative Stomachs" and presented the Society's First Rudolf Schindler Award.

Dr. Roscoe L. Pullen, F.A.C.P., Columbia, Dean of the University of Missouri School of Medicine, was the guest speaker at a meeting of the Tulsa Academy of General Practice on June 28 in Tulsa, Okla. His topic was "Trends Influencing Medical Practice."

In addition to those participants previously reported, Dr. Burton L. Zohman, F.A.C.P., Brooklyn, N. Y., addressed the American College of Cardiology during the annual convention in Chicago on May 29. He spoke on "The Immediate Prognosis of Acute Myocardial Infarction."

Dr. Samuel Bellet, F. A. C. P., Philadelphia, will participate in a seminar on "Cardiac Arrhythmias" and a symposium on "The U Wave" at a meeting of the Vermont Heart Association, Burlington, Sept. 10.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, who was recently appointed a Consulting Editor to the *American Journal of Physiology* and the *Journal of Applied Physiology*, will direct a two-day course for teachers of physiology in Madison, Wis., Sept. 6–7. The subject will be "Pulmonary Physiology" and the course is the first of its kind to be sponsored by the American Physiological Society.

Dr. P. G. Secrest, Jr., F.A.C.P., Long Beach, Calif., was recently installed as President of the Long Beach Heart Association. Dr. Secrest is Clinical Instructor in Medicine at the University of California at Los Angeles; Senior Attending Physician, Harvard General Hospital at Torrance; and a member of the staff of several local hospitals.

Dr. Elliston Farrell, F.A.C.P., and Dr. Donald H. Root, F.A.C.P., were elected Directors of the Association. Among Directors completing unexpired terms are Dr. J. Thomas Hardesty, F.A.C.P., Dr. Frederick Kellogg, F.A.C.P., and Dr. Walter P. Martin, F.A.C.P.

Dr. Orin R. Witter, F.A.C.P., West Hartford, was one of four physicians honored at a recent special ceremony during the annual dinner of the Connecticut State Medical Society in Hartford. He received one of the service pins in token of his fifty years' service as a physician. Born in 1876, Dr. Witter was graduated from Columbia University College of Physicians and Surgeons in 1901 and has been a Fellow of the College since 1925.

Drs. Lazarre John Courtright, F.A.C.P., and Edward Matzger, F.A.C.P., both of San Francisco, were recently elected President and Secretary-Treasurer, respectively, of the Northern California Society of Allergy.

Dr. John J. Andujar, F.A.C.P., Fort Worth, has recently been installed as President of the Texas Society of Pathologists, and Dr. C. B. Sanders, F.A.C.P., Houston, has been chosen President-Elect.

Dr. John R. Paul, F.A.C.P., New Haven, Conn., was recently awarded the Howard Taylor Ricketts Medal of the University of Chicago. The award is made annually as a tribute to the late Dr. Ricketts, who in 1906 proved that Rocky Mountain spotted fever was transmitted by a tick and who three years later discovered the causative organism which has been named after him. Professor of Preventive Medicine at Yale University School of Medicine, Dr. Paul has studied epidemics of poliomyelitis in Alaska, Egypt, Japan, and the tropics, as well as infectious hepatitis among the troops in Germany. Director of the Virus and Rickettsial Commission of the U. S. Army Epidemiological Board, Dr. Paul received the College's John Phillips Memorial Medal in 1942.

Dr. Howard A. Rusk, F.A.C.P., New York City, recently received the annual award of the Save the Children Federation "in recognition of distinguished and devoted service in the field of health and welfare for children." At the same time, Dr. Rusk was praised for his work as Associate Editor of the *New York Times* and for his other writings which have made him "a potent force in creating enlightened programs of aid for underprivileged and handicapped children."

Dr. Maurice S. Segal, F.A.C.P., Boston, was the guest speaker at the annual meeting of the American Academy of Tuberculosis Physicians in San Francisco on June 19. His topic was "Chronic Pulmonary Emphysema, Physiopathology and Treatment."

Under the Presidency of Dr. Charles A. Ragan, Jr., F.A.C.P., New York City, the American Rheumatism Association held its annual meeting, June 18–19, in San Francisco. At the invitation of the Association, Dr. Currier McEwen, F.A.C.P., New York City, presented an interim report on "American Rheumatism Association Coöperative Study of Cortisone Therapy in Rheumatoid Arthritis." Drs. Richard H. Freyberg, F.A.C.P., and Edward W. Lowman (Associate), both of New York City, served as respective moderators for panel discussions on "Hormones in Rheumatic Diseases" and "Rehabilitation of the Arthritic Patient."

At the annual meeting of the American Diabetes Association, which was held in San Francisco, June 19–20, Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, served as moderator for a panel discussion, "Diabetes and Pregnancy." Drs. Lester J. Palmer, F.A.C.P., Seattle, Wash., and Priscilla White, F.A.C.P., Boston, were discussants.

Dr. Salvatore P. Lucia, F.A.C.P., San Francisco, was the after-dinner speaker at the banquet held during the annual meeting of the American Geriatrics Society in San Francisco, June 17–19. His address was entitled "Balm for the Autumnal Years." During the scientific sessions, Dr. George C. Griffith, F.A.C.P., Los Angeles, acted as moderator of a panel discussion, "Recent Developments in Cardiology"; Dr. Cornelius P. Rhoads, F.A.C.P., New York City, served as moderator of a panel on "Changes in Steroid Excretion with Advancing Years," and Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., discussed "Hormones, Growth and Senescence."

Dr. John R. Paul, F.A.C.P., New Haven, Conn., delivered the Fifth Annual Don W. Gudakunst Memorial Lecture at the University of Michigan School of Public Health, Ann Arbor, May 5. His subject was "Historical and Geographical Aspects of Poliomyelitis."

Drs. John A. Schindler, F.A.C.P., Monroe, Wis., and Adolph L. Sahs, F.A.C.P., Iowa City, were among the out-of-state speakers at the 59th Annual Convention of the Upper Peninsula Medical Society, which convened June 18–19 in Menominee, Mich. Their respective subjects were "Group Psychotherapy" and "Strokes, Differential Diagnosis."

Dr. E. Cowles Andrus, F.A.C.P., Baltimore, President of the American Heart Association and Associate Professor of Medicine at the Johns Hopkins University School of Medicine, will be the principal speaker at the annual meeting of the West Virginia Heart Association, to be held in Huntington on Nov. 5.

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa., has been appointed by the Board of Regents as official observer of the American College of Physicians to the Eighth General Assembly of the World Medical Association at Rome, Italy, September 26 to October 2, 1954.

Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., was the recipient of a Memorial Medal when he delivered the 1954 Varrier-Jones Memorial Lecture, sponsored by the Board of the Papworth Village Settlement, in London, England, in May.

Dr. Trimble is the first physician chosen outside of England to give the biennial Memorial Lecture. His subject was "Current Treatment of Tuberculosis in the United States." On his way to London, Dr. Trimble was a representative of the American College of Chest Physicians at the Seventh Meeting of the World Health Organization in Geneva; he also addressed the Medical Society of Leysin, Switzerland, and was a guest speaker at the Southwest German Tuberculosis Conference at Wildbad, Germany, May 6–8.

The University of Louisville School of Medicine has recently established three new sections in the Department of Medicine with Dr. Herbert L. Clay, Jr., F.A.C.P., as Chief of Cardiovascular Diseases, Dr. Oscar O. Miller, F.A.C.P., as Chief of Diseases of the Chest, and Dr. Sam A. Overstreet, F.A.C.P., as Chief of Gastroenterology.

Dr. Theodore L. Badger, F.A.C.P., Boston, discussed "Rest, Exercise and Chemotherapy in the Treatment of Tuberculosis" at the 101st Annual Session of the Maine Medical Association, held in Rockland, June 13–15. Dr. Badger's address was sponsored by the Maine Tuberculosis Association.

Dr. O. O. Meyer, F.A.C.P., Madison, Wis., spoke on "The Problem of Nephritis" at the 62nd Annual Meeting of the Idaho State Medical Association, held at Sun Valley, June 13–15.

Dr. Heinrich Necheles, F.A.C.P., Chicago, was a guest of honor at the Fifth Pan American Congress on Gastroenterology, held in Sao Paulo, Brazil, July 19–24. Dr. Necheles also delivered talks at the medical schools of Montevideo, Santiago, Buenos Aires, and in Lima after the Congress.

Dr. Rudolph E. Fremont, F.A.C.P., Brooklyn, N. Y., presented a paper, "Analysis of the Clinical Response and Tolerance of the Elderly Cardiac to Various Digitalis Glycosides," before the International Congress of Gerontology in London, England, July 22.

Dr. Benjamin Jeffries, F.A.C.P., Detroit, has been elected Secretary of the Michigan Society of Neurology and Psychiatry for the year 1954–55.

Dr. Ray L. Casterline (Associate) was released from active duty in the Medical Corps of the U. S. Navy on May 31, 1954, and returned to the active practice of Internal Medicine and Cardiology in partnership with Dr. Homer Rush, F.A.C.P., Portland, Ore., on July 1, 1954.

Maj. Gen. Harry G. Armstrong, Surgeon General of the U. S. Air Force and College Governor for the U. S. Air Force, terminated his tour of duty as Surgeon General on July 1 and assumed the new duties as Surgeon of the U. S. Air Forces in Europe. He was succeeded by Maj. Gen. Dan C. Ogle, F.A.C.P., as Surgeon General, Gen. Ogle assuming his duties on July 15.

Dr. Walter B. Frommeyer, Jr. (Associate), Birmingham, was appointed Associate Dean of the Medical College of Alabama on July 1. Chief of Medicine at the Veterans Administration Hospital in Birmingham, Dr. Frommeyer succeeded Dr. James O. Foley, who at his own request returned to his former position as Professor and Chairman of the Department of Anatomy of the Medical College.

Dr. Edgar Hull, F.A.C.P., New Orleans, has recently been appointed Associate Dean of Louisiana State University School of Medicine. Dr. Hull has been Professor of Medicine and Head of the Department and is the only member of the original faculty of the School of Medicine who is still teaching.

Dr. Zolton T. Wirtschafter, F.A.C.P., Portland, has recently been named Assistant Clinical Professor at the University of Oregon Medical School. Dr. Wirtschafter is also Chief of Medical Service at the Veterans Administration Hospital in Portland.

Dr. J. Roscoe Miller, F.A.C.P., Evanston, Ill., President of Northwestern University, has recently been elected a member of the Board of Directors of G. D. Searle & Co.

Dr. Jerome M. Swarts (Associate), Memphis, has recently been appointed Assistant Professor of Medicine at the University of Tennessee College of Medicine.

Dr. Michael M. Dacso (Associate), New York City, was invited to read a paper before the Third International Gerontological Congress in London in July. The title of his paper was "Changes in the Circulation of the Hemiplegic Extremities—an Experimental and Clinical Study."

Dr. Dacso has surveyed some of the rehabilitation facilities for the State of Idaho on the invitation of the Medical Care Interim Study Committee of the state, and will submit a detailed report of his findings to the committee.

Drs. James H. Currens, F.A.C.P., Boston, and Henry A. Schroeder, F.A.C.P., St. Louis, were among the panel members who discussed "Treatment of Hypertension" at the 101st Annual Meeting of the Minnesota State Medical Association in Duluth, June 7–9. The panel was moderated by Dr. Richard M. Shick, F.A.C.P., Rochester.

Drs. Leo H. Criep, F.A.C.P., Frank J. Gregg, F.A.C.P., and Robert L. Forsyth (Associate), members of the faculty of the University of Pittsburgh School of Medicine, were the principal guest speakers at a regional meeting of the West Virginia Academy of General Practice, which was held in Weirton on June 13. Their respective subjects were "The Management of the Asthmatic Patient," "Coronary Heart Disease," and "Renal Disease."

Dr. Criep also spoke on "Allergic Pulmonary Disease" at an all-day meeting of the Preston County (W. Va.) Medical Society on June 17.

In addition to those previously reported as participating in the Seventh World Health Assembly, held in Geneva, Switzerland, in May, Dr. Felix Hurtado Galtés, F.A.C.P., Havana, was the chief delegate from Cuba.

Dr. Daniel Blain, F.A.C.P., Washington, D. C., Medical Director of the American Psychiatric Association, delivered the concluding lecture of the series on treatment in psychiatry at the North Shore Health Resort, Winnetka, Ill. His subject on June 2 was "The General Practitioner Can Contribute Toward Healthy Emotional Development." Dr. Blain also discussed "Psychiatry for the General Practitioner" and gave the banquet address at the 51st Annual Meeting of the Wyoming State Medical Society, which met in Sheridan, June 7–9.

At the regular monthly meeting of the Kanawha Medical Society, held in Charleston, W. Va., May 11, Dr. Joseph H. Fries, F.A.C.P., Brooklyn, N. Y., presented a paper on "Current Methods of Management of Severe Allergic Reactions to Penicillin and Other Injected Therapeutic Substances."

Dr. Paul György, F.A.C.P., Philadelphia, who will receive a Borden Award, will be one of the principal speakers at the 23rd Annual Meeting of the American Academy of Pediatrics, to be held in Chicago, Oct. 2–7. Other members of the College who will participate in the Seminars and General Sessions include Drs. Carl V. Moore, F.A.C.P., St. Louis, College Governor for Missouri; Francis E. Senear, F.A.C.P., Benjamin M. Kagan, F.A.C.P., Benjamin M. Gasul, F.A.C.P., and Hans Popper, F.A.C.P., Chicago; Thaddeus S. Danowski, F.A.C.P., Pittsburgh; Richard V. Ebert, F.A.C.P., Park Ridge, Ill.; Gerald M. Cline, F.A.C.P., Bloomington, Ill.; Thomas H. Ham, F.A.C.P., Cleveland; William Dameshek, F.A.C.P., Boston.

A.C.P. Group Insurance Plans Are Still Growing

Health and Accident: The open subscription period closed on June 15. Many members who had not previously submitted applications did so during this second period. 3,605 members have presented applications; growth is very satisfactory. However, it is regretted that more of the members did not avail themselves of the opportunity to secure these benefits while they were available. Members can still subscribe, but will be subject to review of their health history, whereas during the open period no member could be refused coverage, providing he was at the time engaged in active work. The loss ratio continues to be exceptionally favorable. The first two months of the new policy year following April 15, 1954, have produced claims at about the same rate as for the same period during the first year.

Malpractice: Each month more members join this Plan; the growth is steady, but there should definitely be an increased percentage of the members on the Plan. The objective is to obtain at least 50% of member participation. When your present policy comes up for renewal, be sure to compare the new rates quoted you on your old plan with the rates of the A.C.P. Group Plan. It is believed that the A.C.P. rate will be lower, and you are urged to support the College Plan with advantages accruing to you and to other members. Not a single claim has been filed against a member of the College; it is hoped that this perfect record will continue.

Dread Disease: This new Group Plan has proved to be very well received and to answer the needs of many members. At this report (June 28, 1954), almost 1,100 members have subscribed. Many secured protection for children who have already passed their 21st birthday, as well as younger children and themselves. The Plan is still open to subscription through July 15, and it is anticipated that many more applications will be received.

Extension of Benefits to 10 Years for Sickness Disabilities: The Association Service Office since the Annual Session in April distributed a questionnaire to holders of the Health and Accident Insurance Plan to determine how many were interested in having their sickness disabilities extended from 5 to 10 years. About 2,000 replies were received and the tabulated results show that about 75% favor the increased period of benefits; 7% are undecided; and the balance have no interest in the subject. The Association Service Office will try to secure favorable underwriting for this added benefit for those who want it and will attempt to have it available on the next premium due date, October 15, 1954.

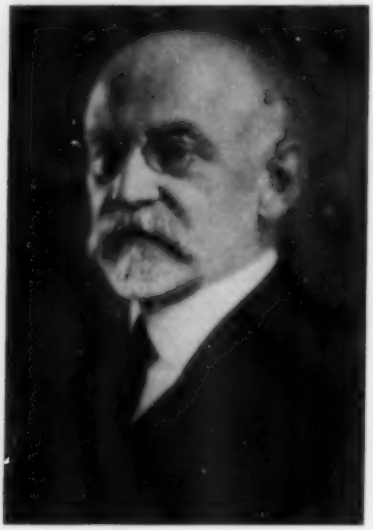
Insurance Advantages to Life Members

All group medical society health and accident plans provide that the physician shall be eligible to hold his policy so long as he is an active member of that society, and usually limit the renewal period to age 70. Translated into practical terms, a physician who is a member of an insurance plan through his county medical society becomes ineligible to continue that insurance if he moves to another community, either outside that county or outside that state. The same principle applies to the physician who has an insurance plan through his state society. Should he remove to another state and terminate his membership in that society, he is no longer eligible to continue the group health and accident insurance plan of that society.

A physician who has become a Life Member of the American College of Physicians, a national society covering North America, remains perpetually eligible, within age limitation, regardless of where he lives and practices. It is true that at time of election to Fellowship in the College, if he were not a full-time teacher or research worker, he would have to be a member of his county and state medical societies and the American Medical Association. However, later termination of membership in county, state and national societies would not affect his Life Membership status in the American College of Physicians and he would be eligible to retain his American College of Physicians Insurance Plans regardless of membership in other societies, once he has become a Life Member. While membership in the American College of Physicians is restricted to citizens of North American countries or their dependencies, there are no restrictions on his place or location of residence and practice. Thus, if he is insured under the A.C.P. Plan, he is covered regardless of where he may be in the world.

OBITUARIES

DR. JAMES B. HERRICK



Dr. James Bryan Herrick, M.A.C.P., Chicago, died March 7, 1954, at the age of 92 years. He was born in Oak Park, Ill., Aug. 11, 1861.

Much has been written about this great American physician who graduated from Rush Medical College in 1888. It is fair to state that Dr. Herrick is Rush's most distinguished graduate as a practitioner, teacher, and clinical investigator. In scholarship, broad culture, scientific competence, thoroughness, and integrity, he was unsurpassed.

He was the great physician—a master of internal medicine. While he made great contributions to our knowledge of coronary artery disease and sickle cell anemia, he always kept a broad vision and interest in the whole field of internal medicine. Patients and doctors alike loved him and were devoted to him. During his active professional life, he was always a top-level consultant in internal medicine, and made numerous contributions to the literature with books, monographs, and individual articles. But with all his great scholarship and culture, he always kept the common touch with all people; he always kept his feet on the ground; he always seemed to be at the grass-roots level with his patients, regardless of their background.

Dr. Herrick was a founder of the Chicago Society of Internal Medicine, the Society of Medical History of Chicago, the Institute of Medicine of Chicago, the Chicago Heart Association, and the American Heart Association. At various times he was President of the American Association of the History of Medicine, the Association of American Physicians, the American Heart Association, and the Congress of American Physicians. In 1939 he received the Distinguished Service Medal of the American Medical Association.

Dr. Herrick held honorary degrees from the universities of Michigan, Chicago, and Northwestern. He became a Master of the American College of Physicians in 1940, had been a Fellow since 1929, served as First Vice President during 1938–39, and was a member of the Board of Regents for eight years (1930–38).

At the time of his death, he was certainly the Dean of all American Internists—the Senior Elder Statesman of American Medicine. Above and beyond his scientific achievements, however, we will remember Dr. Herrick for his great character. His philosophy may be epitomized in a point of view which he borrowed from John Buchan (Lord Tweedsmuir), the distinguished Governor General of Canada, who has joined the great majority with Dr. Herrick. The world needs more of the three "H's"—first, a real interest in people, humanity; second, humility (so we can realize our limitations at all times and all ages); and the third, a sense of humor, an ability to look at ourselves and not to take ourselves too seriously. I think Dr. Herrick would pray with us when we say:

"O Lord, give us the serenity to accept what we cannot change, give us the courage to change what we can change, and give us the wisdom to distinguish between the two."

Dr. Herrick is buried near his summer home at Dorset, Vt. He spent many summers there with his family and his friends in the place that he loved. He is survived by his loving and devoted widow, Zellah, to whom he always gave great credit for her help and devotion, and by a son and daughter.

May his soul rest in peace in his beloved Dorset.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. JAMES HOWARD AGNEW

Dr. James Howard Agnew, F.A.C.P., of Houston, Tex., died on March 19, 1954, at his home after a long illness.

Born in Pittsburgh, Pa., in 1884, Dr. Agnew was a graduate of the University of Michigan, having received his A.B. degree in 1907, his M.A. degree in 1908 and his M.D. degree in 1910. Following graduation he successively served, in the University of Michigan Medical School and the University Hospital, an internship, an assistant residency in internal medicine, and instructorships in clinical microscopy and physical diagnosis. In 1914 he became Professor of Medicine in the Medical College of Alabama and physician to the City Hospital of Mobile. After serving as a Major in the U. S. Army Medical Corps during World War I at the United States Army Base Hospital at Camp Travis, Tex., and at Evacuation Hospital Number 17, Vladivostok, Dr. Agnew moved to Houston. Here he practiced from 1919 until 1940 when he was forced to retire because of a cerebral hemorrhage.

Dr. Agnew had been an Honorary Member of the Texas Medical Association since 1947; he had been a member of that Association and of the American Medical Association continuously since 1920. He served as Secretary of the Section on Medicine and Diseases of Children of the Texas Medical Association in 1924; he was a former President of the Texas Club of Internists, a Life Fellow of the American College of Physicians, of which he had been a member since 1920, and a Diplomate of the American Board of Internal Medicine. At the time of his death he was an honorary member of the staff of St. Joseph's Hospital, the Methodist Hospital and Memorial Hospital. He was a member of Alpha Tau Omega, Phi Beta Pi, Alpha Omega Alpha, and Sigma Xi fraternities.

Dr. Agnew was a capable physician whose professional career was cut short many years by ill health. A reserved, quiet man, he was held in great esteem by those whose privilege it was to know him.

D. W. CARTER, JR., M.D., F.A.C.P.
Governor for Texas

DR. JOSEPH H. BARACH

Joseph Hayem Barach, M.D., F.A.C.P., Pittsburgh, Pa., was born in Kalvaria, Poland, on March 12, 1882, and died March 7, 1954. He was graduated from the University of Pittsburgh School of Medicine in 1903 and was Resident Physician at Western Pennsylvania Hospital during 1903–05.

He had been Consulting Physician to the Department of Health of Carnegie Institute of Technology since 1910, Associate Professor of Medicine at his alma mater since 1940, and Professor of Clinical Medicine at the School of Dentistry since 1934. He had been Medical Director of the Falk Clinic, which is the outpatient department of the Medical Center Hospitals, since 1930. He was also a member of the staffs of the Elizabeth Steel Magee, Woman's, and Eye and Ear Hospitals of the

Medical Center, University of Pittsburgh. He had been Visiting Physician to the Presbyterian Hospital since 1910.

During World War I, Dr. Barach was a Captain in the Army Medical Corps, where he served as a specialist in the cardiovascular division, 1917–18. During World War II he served on the Pittsburgh Selective Service Board No. 1.

In 1940, at the World's Fair in New York, his name was inscribed on the Wall of Fame as "One of the American citizens of foreign birth who has made notable contributions to our living, ever-growing democracy devoted to peace and freedom."

With the United States Public Health Service, he was Chairman (1946–51) of the Metabolic and Endocrinology Section, which steered the spending of grants for research in these fields. As an outstanding authority in the field of metabolism, he was appointed in 1952 as a member of the National Advisory Council on Arthritis and Metabolism of the Public Health Service.

Dr. Barach was associated with Dr. Heinrich Stern in the formation of the American College of Physicians and was an active member since 1917. He was also one of the organizers of the American Diabetes Association and served as Treasurer and later as Vice President. He was President of the American Diabetes Association from 1944 to 1946. He served on the council of this group from 1940 until his death. For his work in the field of diabetes, he was awarded the Frederick G. Banting Medal by the American Diabetes Association.

Dr. Barach always had a broad interest in medicine in general and in clinical investigation in particular. He was the author of 150 original contributions to the medical literature of this country and abroad. His contributions began in 1905 and covered such fields as typhoid fever, blood morphology and the principles of physiology of physical signs in the chest. Later he became interested in cardiovascular disease and wrote on the effects of severe exertion and exercise on heart and blood pressure. This led to articles on blood pressure and neurocirculatory asthenia.

His chief interest lay in the field of diabetes. In 1923, Dr. Barach was one of the first researchers in this country to be given insulin for clinical trial. He reported his first observations with insulin in 1923 in 100 cases, at which time he advocated abandonment of the high fat diet and adoption of normal standards in the treatment of diabetes. Many articles on diabetes followed this one, including two books, *Diabetes and Its Treatment* and *Food and Facts for the Diabetic.*

C. Howard Marcy, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. HENRY T. CHICKERING

Dr. Henry Thorndike Chickering, F.A.C.P., died on March 14, 1954, of a myocardial infarction.

He was born in Lowell, Mass., on June 26, 1885. He received his A.B. from Harvard University in 1907 and his M.D. from Harvard University Medical School in 1911. He was an Intern at Presbyterian Hospital in New York City from 1912 until 1914 and an Assistant Resident and Resident in the Hospital of the Rockefeller Institute for Medical Research in 1914 to 1919. He was Chief of the Tuberculosis Clinic and Visiting Physician (1920–39) and Assistant Attending Physician (1939–46) at the Vanderbilt Clinic. Dr. Chickering was Assistant Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons, in which position he served from 1927 to 1948, and Assistant Professor of Medicine at New York Post-Graduate Medical School and Hospital from 1930 to 1937. He was Attending Physician to the Fifth Avenue Hospital from 1928 until 1937 and to the New York Nursery and Child's Hospital from 1930 to 1937. He was Assistant Attending Physician at the Presbyterian Hospital from 1939 to 1946.

Dr. Chickering was well known for his work and publications concerning respiratory diseases. He was a Diplomate of the American Board of Internal

Medicine, a member of the New York County Medical Society, New York Academy of Medicine, The Harvey Society, American Medical Association, and the American Society for Clinical Investigation. He became a Fellow of the American College of Physicians in 1931.

Dr. Chickering was well known to the medical profession of New York and had many friends and admirers throughout the United States. A careful student and practitioner of internal medicine, he was beloved by his friends and colleagues, who note his passing with sincere regret.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

CDR. THOMAS F. DUHIGG, (MC), USN, RETIRED

Cdr. Thomas Francis Duhigg, (MC), USN, Retired, F.A.C.P., died at the Naval Hospital, St. Albans, N. Y., on May 26, 1954. He was 76 years old.

Born in Des Moines, Iowa, March 10, 1878, Cdr. Duhigg received his Doctor of Medicine degree from Jefferson Medical College of Philadelphia in 1902. He was commissioned a Lieutenant, junior grade, Naval Reserve Force in 1917, and was discharged to accept a Regular Navy commission in 1918. He was placed on the Retired List of Officers of the Navy in 1940, and retained on active duty until December, 1944. He was commissioned a Commander in 1942.

Prior to entering the Navy, Cdr. Duhigg served during the Mexican Border Incident as a Major, (MC), USA, Commanding Officer of Iowa Field Hospital No. 1, having graduated from the Army Medical School in 1906.

During his nearly thirty years of Naval service, Cdr. Duhigg served at the Receiving Stations at Boston, Mass., and Norfolk, Va.; at the Marine Barracks, Parris Island, S. C.; with the Fifth Regiment, Second Brigade, U. S. Marines in Nicaragua; and at the Recruiting Stations, Des Moines, Iowa; Boston, Mass.; Louisville, Ky.; and Brooklyn, N. Y. He also served aboard the United States Ships *Aberenda, Sacramento, Helena* and *Asheville*. During World War II, he served with V-12 Units at Middlebury (Vt.) College; University of Vermont, Burlington; Tufts College, Medford, Mass.; and Boston University School of Medicine. His final tour of duty was with the Veterans Administration in New York City.

A Diplomate of the American Board of Internal Medicine, Cdr. Duhigg was a former President of the Des Moines Pathological Society and had served for ten years as Treasurer of the Polk County (Iowa) Medical Society. In addition, he had been Treasurer of the Iowa State Medical Society from 1915 until 1922. Cdr. Duhigg was elected to Fellowship in the American College of Physicians in 1935.

Graveside services were held in Arlington Cemetery, Washington, D. C., on June 1, 1954.

Technical Information Office,
Bureau of Medicine and Surgery,
Department of the Navy

DR. WILLIAM H. GILLENTINE

Dr. William Howard Gillentine, F.A.C.P., a prominent New Orleans internist, died on April 16, 1954, at Jourdan Acres, Miss. Dr. Gillentine was born Sept. 4, 1908, in Meridian, Miss., but received his early education in New Orleans, La., and Fort Myers, Fla.

He received his Bachelor of Science degree from Tulane University in 1930 and a Doctor of Medicine degree from Tulane University of Louisiana School of Medicine in 1932. He served an internship at Charity Hospital of Louisiana at New Orleans from 1932 to 1933. From 1933 to 1934 he served as Assistant Instructor and from 1934 to 1936 as a full-time fellow in the Department of Medicine at Tulane

medical school. From 1936 he was an active member of the Department of Medicine of Tulane and at the time of his death held the rank of Assistant Professor of Clinical Medicine.

Dr. Gillentine was elected a Fellow of the American College of Physicians in 1941. He was actively engaged in the practice of internal medicine in New Orleans at the time of his death. He was a member of the staffs of Southern Baptist Hospital, Touro Infirmary, and Charity Hospital of Louisiana, and a medical consultant at the Eye, Ear, Nose and Throat Hospital. He was a Diplomate of the American Board of Internal Medicine.

Dr. Gillentine was an active member of the Orleans Parish Medical Society, Louisiana State Medical Society, American Medical Association, American Diabetes Association, and Southeastern Clinical Club. He served as President of The New Orleans Graduate Medical Assembly in 1947. During World War II he was Medical Director of the National Youth Administration of Louisiana. Dr. Gillentine was also a member of the Rotary Club, Pickwick Club, Metairie Country Club, Theta Kappa Psi medical fraternity and held honorary membership in Alpha Omega Alpha medical fraternity.

In 1933 he and Dr. M. E. DeBakey invented the Simplex Transfusion Set, which was widely used for a time in the administration of direct blood transfusions.

Dr. Gillentine enjoyed a wide circle of friends and acquaintances and was held in high esteem by his colleagues, friends and students. It is with sincere regret that we record the passing of Dr. William Howard Gillentine.

J. O. Weilbaecher, Jr., M.D., F.A.C.P.

DR. SIDNEY D. KLOW

A coronary attack took the life of Dr. Sidney Deutsch Klow (Associate) on May 24, 1954. Though only 45 years old at the time of his death, Dr. Klow had already established himself as one of the leading psychiatrists of the South. He was Assistant Professor of Psychiatry at the University of Tennessee College of Medicine and Chief of the Psychiatry and Neurology Service at the Veterans Administration Hospital in Memphis.

Dr. Klow was born in Chicago on June 27, 1908. After acquiring a B.S. degree at the University of Illinois, he earned his M.D. degree in 1933 at the medical college of that university. Following an internship at the Edgewater Hospital in Chicago, he entered general practice. His major interest from the beginning, however, was psychiatry, and he took an entire year out of his practice to do postgraduate study in this field at Washington University in St. Louis. In 1939 he accepted an appointment to the staff of the Elgin (Ill.) State Hospital. Here he remained until he entered the Army in 1943. Commissioned as a Lieutenant, he was promoted first to Captain, later to Major. He served in the Pacific Theatre, originally as a ward officer, then as psychiatrist to a general hospital, later as psychiatric consultant to the base, and finally as commanding officer of a station hospital.

After leaving the service in 1946, Dr. Klow resumed his post at the Elgin State Hospital and in 1949 accepted appointment to the Veterans Administration Hospital in Memphis. The following year he became Assistant Chief of the Psychiatry and Neurology Service at that hospital and in 1953 was made Chief of the Service.

He became an Associate of the American College of Physicians a few months prior to his death. He was a Fellow of the American Psychiatric Association and a Diplomate of the American Board of Psychiatry and Neurology.

J. T. Boone, Vice Admiral (MC), U. S. Navy, Rtd.,
Chief Medical Director,
Governor for the Veterans Administration

DR. JOHN M. McEACHERN

Dr. John McFaul McEachern, F.A.C.P., died suddenly in the Winnipeg General Hospital on March 20, 1954. He was born in Elmvale, Ont., Can., on March 26, 1896.

At the age of nineteen he enlisted as a private soldier in the 43rd Cameron Highlanders of Canada and later was commissioned as a Lieutenant. He served in France during the First World War with the 16th Canadian Scottish Battalion and later with the 27th Battalion.

Returning to Canada in 1919, he studied medicine at the University of Toronto, where he took his medical degree, and did postgraduate studies at Baltimore. Following this he came to Winnipeg, where he was appointed to the staff of the Faculty of Medicine at the University of Manitoba and to the attending staff of the Winnipeg General Hospital, where he developed the Department of Electrocardiology. At the time of his death, Dr. McEachern had the rank of Physician in the Department of Medicine at the Winnipeg General Hospital and was Cardiologist in charge of the Electrocardiographic Department. He was also Cardiologist and Consultant at the Misericordia Hospital and Associate Professor of Medicine, University of Manitoba.

Dr. McEachern was the Senior Internist and one of the founders of the Manitoba Clinic. In addition to being a Fellow of the American College of Physicians since 1937, he was a Fellow of the Royal College of Physicians of Canada. He was one of the founders and a Past President of the Canadian Heart Association and was also a member of the American Heart Association. He was a member of the Canadian and Manitoba Medical Associations, the Winnipeg Medical Society, and the Manitoba Club. In June, 1953, he was appointed Honorary Lieutenant Colonel of the Queen's Own Cameron Highlanders of Canada.

Dr. McEachern was an outstanding teacher of internal medicine and cardiology and one of the most valuable members of the Faculty of Medicine in the University of Manitoba. He will be greatly missed by all his colleagues on the Faculty and throughout the profession.

CHARLES H. A. WALTON, M.D., F.A.C.P.,
Governor for Manitoba and Saskatchewan

DR. HERMAN O. MOSENTHAL

Dr. Herman Otto Mosenthal, a Fellow of the American College of Physicians since 1936, died on April 4, 1954, of uremia.

Dr. Mosenthal was born in New York City on July 8, 1878. He received his A.B. degree from Columbia University in 1899 and his M.D degree from Columbia University College of Physicians and Surgeons in 1903. He interned at the New York Hospital from 1903 to 1905 and at the New York Foundling Hospital from 1905 to 1906. He became Assistant, Instructor, and Associate in Biological Chemistry at Columbia University during the years 1908 to 1914. He served as Assistant Instructor in Medicine at Columbia University College of Physicians and Surgeons from 1909 to 1914. Dr. Mosenthal then went to Baltimore to serve as Associate Professor of Medicine at Johns Hopkins University School of Medicine from 1914 until 1918, returning to the post of Associate in Medicine at Columbia University College of Physicians and Surgeons from 1919 to 1920.

He joined the staff of the New York Post-Graduate Medical School and Hospital in 1920 as Professor of Medicine, Attending Physician and Chief of the Department of Metabolism, later becoming Director of the Department. He became Clinical Professor of Medicine at the New York Medical College, Flower and Fifth Avenue Hospitals in 1922. He served as Attending Physician at the Seton Hospital from 1908 to 1910 and as Assistant Visiting Physician of the Presbyterian Hospital from 1911 until 1914. He had also been Consulting Physician to the First Division of

Welfare Hospital and to St. Luke's Hospital in Newburgh. At the time of his death, Dr. Mosenthal was Consulting Physician to the New York Infirmary and the University, Bellevue, Goshen, and Sea View Hospitals, where he had been a member of the staff for many years.

Dr. Mosenthal was the author of many publications. He was President of the American Diabetes Association in 1941–42, and subsequently a member of the Council. He was a member of the Board of Directors of the New York Diabetes Association, and a member of the New York Academy of Medicine, American Medical Association, American Society for the Advancement of Clinical Investigation, the Society of Experimental Biology and Medicine, the American Institute of Nutrition and the Association of American Physicians.

Dr. Mosenthal had a long and fruitful career in the practice and teaching of medicine. He influenced the lives of many young men who have later reached high positions in the profession. It is with profound regret that his disciples, friends and confreres pay their respects upon the passing of this distinguished physician.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN O. PIPER

Dr. John Obed Piper, F.A.C.P., of Waterville, Maine, died after a brief illness on March 22, 1954.

Dr. Piper was born in Bingham, Maine, on July 18, 1881. He was graduated from Bates College with a degree of A.B. in 1903, and received the degree of M.D., C.M. at McGill University Faculty of Medicine in 1910. He did postgraduate work at the University of Pennsylvania Graduate School of Medicine in 1924 and 1925. He served as a First Lieutenant in the Medical Corps, U. S. Army, during World War I, and from 1926 until his death he had practiced in Waterville. He was one of the founders of the Thayer Hospital in that city and was a staff member beginning in 1924. He was Chief of the Medical Staff there from 1932.

Dr. Piper was President of the Kennebec County Medical Society in 1933, President of the Maine Medical Association in 1946, and President of the Maine Heart Association in 1947. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1933.

RICHARD S. HAWKES, M.D., F.A.C.P.,
Governor for Maine

DR. SIDNEY A. PORTIS

Sidney Alexander Portis, M.D., F.A.C.P., died May 24, 1954, in the Johns Hopkins Hospital, Baltimore, Md., two days before his sixtieth birthday.

A native of Chicago, Dr. Portis was graduated from the University of Chicago with the degree of Bachelor of Science in 1916 and in 1918 received his M.D. degree from Rush Medical College. After an internship at Cook County Hospital, he joined the faculty of Rush Medical College in 1920 as Assistant in Medicine and became Associate Clinical Professor of Medicine, University of Illinois College of Medicine, in 1935. For six years Dr. Portis was also Professor of Medicine at Stritch School of Medicine of Loyola University. He joined the staff of the Michael Reese Hospital in 1920 as Assistant in Medicine and at one time was Assistant Director of the Hospital's Emanual Mandel Dispensary, later becoming Senior Attending Physician in the Department of Internal Medicine and Medical Chief of the Psychosomatic Group of the Institute for Psychosomatic and Psychiatric Research and Training. He had also been Attending Physician and Consulting Physician at Cook

County Hospital for a number of years, and during 1929–31 he was Senior Attending Physician (Private Service) at Mercy Hospital.

Within the past two years, Dr. Portis had moved from Chicago to California, where he was a member of the staff of the Beverly Hills Clinic. Since becoming a Fellow of the College in 1929, he had always taken an active interest in the affairs of the College and enthusiastically contributed to the success of the Southern California Regional Meeting last February.

A Diplomate of the American Board of Internal Medicine, Dr. Portis was a member of the Advisory Board of the Institute of Psychoanalysis and was Associate Chief Examiner, Subsidiary Board, National Board of Medical Examiners. He was the author of numerous articles and essays; and in 1941 under his editorship, the first edition of *Diseases of the Digestive System* was published.

Local Chicago societies of which he was a member included the Chicago Medical Society, Chicago Pathological Society, Chicago Society of Internal Medicine, Chicago Roentgenological Society, and the Institute of Medicine of Chicago. In addition, Dr. Portis was a member of the Illinois State Medical Society, American Medical Association, American Gastro-Enterological Society, Radiological Society of North America, Society for Experimental Biology and Medicine, American Psychosomatic Society, Central Society for Clinical Research, and the Mississippi Valley Medical Society. He was also an honorary member of the Mexican Association of Gastro-enterology.

It is with regret that the passing of Dr. Portis is noted at this time.

DR. HERBERT L. REYNOLDS

Dr. Herbert Lindley Reynolds, F.A.C.P., died of a myocardial infarction on Feb. 19, 1954, in Atlanta, Ga.

A native of Georgia, Dr. Reynolds was born in Marietta on Aug. 26, 1884. He received his A.B. degree from the University of Georgia and graduated from the Emory University School of Medicine in 1909. He then interned at Grady Memorial Hospital, Atlanta, until 1911. He began the practice of internal medicine in Atlanta after the completion of his internship and was active in teaching in the medical school. In 1917-18 he served his country in the Medical Corps of the U. S. Army with the rank of First Lieutenant.

After the cessation of hostilities, Dr. Reynolds resumed his practice and teaching activities. He became Assistant Professor of Medicine at Emory and later was made Associate Professor of Clinical Medicine. He was regarded by the students as one of the most capable teachers in the school.

Dr. Reynolds became a Fellow of the College in 1926, and for twenty years thereafter he regularly attended the Annual Sessions.

In 1946 Dr. Reynolds was forced to retire because of his health. His retirement was keenly felt by his patients, fellow practitioners, and students as he was regarded as one of the community's most capable internists and teachers.

Dr. Reynolds was a Diplomate of the American Board of Internal Medicine. He was a member of the Fulton County Medical Society, the Medical Association of Georgia, the American Medical Association and the Association for the Study of Internal Secretions. He was also a member of the Kappa Alpha college fraternity and the Chi Zeta Chi Medical Fraternity. He was a communicant of the Episcopal Church.

Dr. Reynolds is survived by his wife and two sons. He will be greatly missed by his family, colleagues, patients and friends.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. WILLIAM HENRY ROBEY

On Feb. 23, 1954, Dr. William Henry Robey, F.A.C.P., died at the age of 83 years. Actively engaged in the practice of medicine until shortly before his death caused by coronary thrombosis, Dr. Robey's passing took from our medical community one who exemplified the best of the precepts of medical teaching of the past and one whose contributions to his profession revealed the constant assimilation and application of the advances of current medical progress.

Dr. Robey was born in Boston, July 3, 1870, attended Harvard College and received from the Harvard Medical School his M.D. in 1895. Between the years of 1894–96 he served as House Pupil at the Boston City Hospital, subsequently at the Boston Lying-In Hospital. He entered the practice of medicine in 1897; and from 1900, when he became a member of the teaching staff of the Harvard Medical School as Assistant in Bacteriology, until 1932 when he retired from active teaching as Clinical Professor of Medicine, Emeritus, he was an active and colorful member of the faculty of his alma mater. In 1930 he was honored by being named the George W. Gay Lecturer for the Harvard Medical School.

At the Boston City Hospital he served as Visiting Physician and was Chief of the Second Medical Service. He was Consulting Physician to the Norwood Hospital, Marlborough Hospital and the Milton Hospital and Convalescent Home. He was formerly Visiting Physician to the Boston Dispensary.

During World War I he first served as Major in the Medical Corps and Chief of the Medical Service at Camp McClellan. As Lieutenant Colonel he was Consultant in Medicine of the Advance Sector, A.E.F., and, as Colonel, commanded the Seventh Hospital Center.

His professional publications were numerous, for the most part dealing with problems of circulation and cardiology. The list of the professional societies of which he was a member, in many of which he served as an officer, reveals, the breadth of his clinical interest and reflects the esteem with which he was held by his fellows. He was a member of the American Heart Association, serving as its Vice President in 1927–29 and President in 1929–31. In 1948 he was made an Honorary Life Member of that organization and was a member of the Founders' Group for Scientific Research. In the fall of 1953 he was honored by the Association presenting him with its Silver Medallion Distinguished Service Award. He also served as President of the New England Heart Association between 1927–29. In 1929 he was Shattuck Lecturer for the Massachusetts Medical Society and was President of that Society from 1933–35. He became a Fellow of the American College of Physicians in 1929 and was also a Fellow of the American Association for the Advancement of Science. He was a member of the American Association of Pathologists and Bacteriologists, the American Clinical and Climatological Association and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine.

To list merely the formal appointments and society affiliations of Dr. Robey is to do but scant justice to his memory. His ready wit and frequently interpolated stories colored his formal lectures and addresses with his personality—so well and so affectionately recalled by his former students and listeners. Dr. Robey never forsook a manner of fundamental dignity and with it a warmth of friendship which all who knew him valued and respected. It is the privilege of few to engage in the active practice of medicine for 56 years, and it is indeed rare to see one's later years marked with the physical and mental alertness and energy which characterized Dr. Robey. His passing occasions the deepest regrets of his many friends and admirers and their sincerest sympathy extends to Mrs. Robey and his son who survive him.

RICHARD P. STETSON, M.D., F.A.C.P.,
Governor for Massachusetts

REPORT OF MEETING OF THE BOARD OF GOVERNORS

April 6, 1954

Fifty-seven members of the Board of Governors, or their Alternates, attended a regular meeting at Chicago on April 6, 1954, at the Conrad Hilton Hotel, under the Chairmanship of Dr. Charles A. Doan.

Guests at the meeting included President Cyrus C. Sturgis, Ann Arbor, Mich., and Dr. John Hinman, Hospital Inspector for the American College of Physicians on the Joint Commission on Accreditation of Hospitals, and Dr. LeRoy H. Sloan, Chicago, Ill., retiring President of the College.

President Sloan presented a recommendation that consideration be given to the promulgation of a set of rules with reference to the handling of Regional Meetings, especially in regard to the entertainment of official officers from the College.

The possibility of dividing the New England States into two groups for Regional Meeting purposes was discussed, but due to the fact that the New England Regional Meeting is already set up for the autumn of 1954, consideration of this possibility was delayed.

At the invitation of Chairman Doan, Dr. T. Grier Miller, Chairman of the Regents' Committee on Membership, presented a report recommending a serious consideration of revising the types of membership in the College, eliminating Associateship and having all members elected in the future on a permanent basis as Fellows. The specific recommendations were as follows:

"(1) That steps be taken to provide that all future admissions to membership in the College be as Fellows. If this recommendation is approved, the Committee anticipates that most of the present Associates in due time will become Fellows;

"(2) That the Associates not elected to Fellowship be continued on a permanent basis as Associates, as have some who originally were members of the American Congress on Internal Medicine;

"(3) That if Associateship for future candidates is abandoned, the criteria for Fellowship be defined as follows:

(a) The candidate shall be graduated from a medical school acceptable to the Board of Regents at least five years previously;

(b) If engaged in practice, his professional activities shall be confined to the field of Internal Medicine or a related specialty;

(c) He shall be certified by the national Board of Certification in his particular field, when such a Board exists, or have had an equally adequate background of training and experience;

(d) He shall have demonstrated to the satisfaction of the Committee on Credentials a keen interest in the progress of medicine. Special consideration shall be given to those who, as practitioners, teachers, investigators or administrators, have made noteworthy contributions;

(e) His character shall be above reproach. He shall have emotional stability, good judgment and social adaptability. For an evaluation of these attributes, his general reputation and the opinions of his medical confreres, and especially of his local Governor and such a screening committee as the Governor may designate, shall be relied upon."

These recommendations were submitted for general discussion to the Board of Governors, prior to being presented to the Board of Regents for more serious con-

sideration. There was much difference of opinion expressed, but after prolonged discussion, there were 47 voting in favor of the motion and 9 opposed. This merely was an indication of sentiment to be carried to the Board of Regents later.

Dr. Cyrus C. Sturgis, Chairman of the Committee on Fellowships and Awards, announced to the Governors the names of the recipients of the Mead Johnson Postgraduate Scholarships, namely, Dr. Joseph F. Dingman (nominated by Governor Richard P. Stetson, Massachusetts), Dr. Morton Bogdonoff (nominated by Governor Elbert L. Persons, North Carolina), and Dr. Leighton E. Cluff (nominated by Governor R. Carmichael Tilghman, Maryland).

A progress report form to be used by Governors in checking the progress of Associates toward fulfilling the requirements for Fellowship, subject to individual variations, was adopted.

An evaluation questionnaire to be distributed by each Governor to 4 or 5 of the members from his area was adopted, the purpose being to evaluate the various features of the Annual Session Program, the forms to be distributed by the Governor and collected by the Governor and transmitted to the Executive Secretary for the attention of the Committee on Educational Policy.

Dr. Lemuel C. McGee, Governor for Delaware and Marshal of the College, reported on changes in the Convocation procedures that had been adopted for the 1954 Convocation.

The Governors reviewed a service certificate, which the Regents of the College proposed to issue to all past officers, past Regents and past Governors of the College, the recommendation having first emanated from the Board of Governors a year ago. Considerable discussion was initiated concerning the manner of nominating Governors as replacements of those who resign or retire after their maximum period of service. It was the consensus that the Committee on Nominations should not be bound by a hard and fast rule in the manner in which they decide on nominations of Governors, the technique left to the discretion of the area and circumstances involved. However, the Committee shall be free to contact members at large, individually or by ballot, to consult the current Governor for information and to proceed much in the manner in which the current Committee has operated.

Dr. Thomas M. McMillan, Chairman of the Committee on Postgraduate Courses, made a detailed report on courses that have been concluded and on the schedule of courses recommended for the autumn of 1954, the spring of 1955, and partially on the proposed schedules thereafter.

Dr. Walter L. Palmer, Chairman of the Editorial Board of the ANNALS OF INTERNAL MEDICINE, discussed with the Governors numerous points affecting policy in the publication of the journal, and reported a proposal that the News Notes section may be published as a separate bulletin of the College. While decision would be made by the Board of Regents, many Governors were adverse to eliminating the News Notes section from the journal.

Announcement was made that the 1955 Annual Session of the College would be held at Philadelphia, April 25–29, and the cities under consideration for 1956 were mentioned, but no specific preference was voted.

Appreciation of the College for his long period of service was extended to Dr. John W. Scott, College Governor for Alberta, whose term expired at this meeting.

Dr. Robert Wilson was reëlected for a three-year term as a representative of the Board of Governors on the Committee on Credentials, to serve until 1957.

Dr. Ellsworth L. Amidon, Governor for Vermont, was elected a member of the Committee on Credentials to fill out the unexpired term of Dr. J. Murray Kinsman, until 1955.

Dr. Carter Smith, Governor for Georgia, was elected Chairman of the Board of Governors for a term of three years, and Dr. William C. Menninger, College Governor for Kansas, was duly elected Vice Chairman for a term of three years.

A resolution was adopted providing that in the future, dress for the Reception and Dinner to New Members shall be "informal."

The meeting closed with a statement of appreciation on the part of the retiring Chairman, Dr. Charles A. Doan, for the coöperation and support of the Governors during his term as Chairman.

REPORT OF MEETING OF THE BOARD OF REGENTS

April 7, 1954

The second meeting of the Board of Regents of the American College of Physicians, during the 35th Annual Session, was held at Chicago, April 7, 1954, with President LeRoy H. Sloan presiding and Mr. E. R. Loveland acting as Secretary. Present were 18 members of the Board and the Chairman of the Committee on Postgraduate Courses.

After a lengthy discussion of the matter of an exchange of representatives among the American College of Physicians, the Royal Australasian College of Physicians and the Royal College of Physicians of London, the incoming President was authorized to appoint a committee to discuss and investigate all aspects of the matter. Dr. Cyrus C. Sturgis, the incoming President, subsequently appointed a committee, consisting of Dr. George F. Strong, Chairman, Vancouver; Dr. Herbert K. Detweiler, Toronto; Dr. T. Grier Miller, Philadelphia; Dr. Maurice C. Pincoffs, Baltimore; the incoming President to be a member ex officio.

By resolution, the Regents adopted the following regulations governing travel expenses.

"Officers, Regents, Governors or Members of the College when required to travel on special duties assigned by action of the Board of Regents: Round trip train and roomette (or equivalent) fares, plus meals, not exceeding $10.00 per day while en route, plus living expenses during stay while on College business at place of meeting not to exceed $25.00 per day.

"Officers and Regents attending Annual Sessions: Round trip train and roomette (or equivalent) fares only.

"Specially Invited Guest Speakers at Annual Sessions: Round trip train and roomette (or equivalent) fares, plus meals not exceeding $10.00 per day while en route, plus living expenses for the day or days on which their papers are presented, not to exceed $25.00 per day.

"Governors attending Annual Sessions: One-half round trip train and roomette (or equivalent) fares only."

Growing out of the recommendations of a special Reference Committee on Blue Shield and related subjects, said Committee having been headed by Dr. William C. Chaney, the following resolution was adopted and a Committee continued for the purpose of further investigation:

"Whereas, the American College of Physicians is deeply interested in maintaining the highest standards of medical practice for the benefit of all patients, and

"Whereas, the recent rapid growth of prepaid voluntary insurance coverage to meet physicians' fees could result in significantly affecting the quality of medical practice because no adequate provision is made in such insurance coverage for the proper remuneration of medical specialists, including internists,

"THEREFORE BE IT RESOLVED: (1) That the American College of Physicians approve in principle a voluntary prepaid insurance coverage to meet physicians' fees, and (2) that a Committee be appointed by the President of the College to study such insurance coverage and to present to the Officers and Regents appropriate recommendations for its improvement, to the best interests of the patients and the equitable remuneration of the attending physicians."

Dr. Wallace M. Yater, who had been appointed as a Committee of one to investigate the propriety of the American College of Physicians endorsing educational, medical films and to participate in an advisory or consulting capacity on their production, presented relevant information and data following which a resolution was adopted authorizing the incoming President to appoint a Committee on Medical Educational Films, for the purpose of passing upon new films as they are in production and in which the College is interested, regardless of the producer, the Committee to function only on request. Subsequently, the incoming President, Dr. Cyrus C. Sturgis, appointed the following Committee: Dr. Wallace M. Yater, Washington, Chairman; Dr. T. Grier Miller, Philadelphia; Dr. George Morris Piersol, Philadelphia.

Dr. T. Grier Miller, Chairman of the Committee on Membership, made a follow-up report on the study made by the Committee on the representation of A. C. P. members on the medical staffs of the medical schools of this country and Canada. It was revealed that there has been an increasing number of medical teachers who have become affiliated with the College since the survey was first undertaken. The Committee had extended its studies to the matter of types of membership in the College, and presented the following arguments in favor of eliminating Associateship and having all members elected in the future on a permanent basis as Fellows:

"(1) The prestige of membership would be enhanced, every member being entitled to all the privileges of the College.
"(2) The disappointment and sometimes the antagonism of Associates dropped from membership and of their sponsors would be avoided. Such a reaction would seem all the more likely to occur now that a ten-year period of temporary membership as an Associate is permissible.
"(3) Only a single survey of each candidate by the Committee on Credentials would be required. This is significant in view of the steadily increasing number of candidates.
"(4) Complications of administration incident to a steadily increasing number of Associates, almost certain eventually to exceed the number of Fellows, would be obviated."

Disadvantages:

"(1) A financial loss to the College would result.
"(2) The opportunity for the training and indoctrination of candidates for Fellowship would be lost."

Specific recommendations of the Committee were:

"(1) All future admissions to membership in the College shall be as Fellows.
"(2) The Associates not elected to Fellowship shall be continued on a permanent basis as Associates, as have some who originally were members of the American Congress on Internal Medicine.
"(3) If Associateship for future candidates is abandoned, the criteria for Fellowship shall be defined as follows:

(a) The candidate shall have graduated from a medical school acceptable to the Board of Regents at least 5 years previously;
(b) If engaged in practice, his professional activities shall be confined to the field of internal medicine or a related specialty;
(c) He shall be certified by the national board of certification in his particular field, when such a board exists, or have had an equally adequate background of training and experience;
(d) He shall have demonstrated to the satisfaction of the Committee on Credentials a sincere interest in the progress of medicine. Special consideration shall be given to those who, as practitioners, teachers, investigators or administrators, have made noteworthy contributions;
(e) His character shall be above reproach, and he shall have emotional stability, good judgment and social adaptability. For an evaluation of these attributes, his general reputation and the opinions of his medical confreres, and especially of his local Governor and such a screening committee as the Governor may designate, shall be relied upon."

There was wide and divergent opinion on the proposal and a resolution was unanimously adopted providing that the matter be deferred until the next meeting of the Board of Regents.

On the recommendation of the Committee on Administrative Organization, authorization and budget appropriations were made for certain administrative changes in the Executive Offices of the College.

Dr. Cyrus C. Sturgis, Chairman of the Committee on Fellowships and Awards, reported in detail on each of the 20 Latin-American Fellows working in this country, on the Research Fellows and the A. Blaine Brower Traveling Scholars. By resolution, the Board of Regents approved recommendation of the Committee on Fellowships and Awards that Mead Johnson Postgraduate Scholarships, administered by the College, be granted to the following, beginning July 1, 1954: Dr. Joseph F. Dingman (nominated by Governor Richard P. Stetson, Massachusetts); Dr. Morton Bogdonoff (nominated by Governor Elbert L. Persons, North Carolina); Dr. Leighton E. Cluff (nominated by Governor R. Carmichael Tilghman, Maryland).

Dr. Thomas M. McMillan, Chairman of the Committee on Postgraduate Courses, gave an extended report on the program completed for the year 1953, and the program for the current semester. He also presented the schedule of courses recommended for the autumn of 1954, the spring of 1955, and partially for periods thereafter, these recommendations being unanimously approved by the Board of Regents. (The outline of courses is not herein published because they have been announced previously and published elsewhere in this journal.)

Growing out of the recommendations of Dr. Asa L. Lincoln, Chairman of the Committee on Public Relations, numerous matters affecting policies were disposed of; the President was authorized to appoint a member of the College to the Medical Advisory Council of the American Occupational Therapy Association; the President was authorized to appoint a committee of 5 to 7 members to study a proposal from the Commission on Organization of the Executive Branch of the Government, Division IV, Medical Services Task Force; dues were waived for 5 members because of incapacitation; the resignations of 2 Associates were accepted; and the resignations of two Fellows were held over for further investigation.

Dr. Walter L. Palmer, Chairman of the Editorial Board of the ANNALS OF INTERNAL MEDICINE, reported there has been a gratifying increase in the number of manuscripts submitted to the Editor each year, 379 during 1953, 217 of these being accepted for publication; that the average interval between receipt and acceptance or rejection of manuscripts had not exceeded 3 months, and that other matters had

been handled most expeditiously by the Editor. He reported further that a Cumulative Index of the ANNALS, as authorized by the Board of Regents at its meeting on November 15, 1953, is in process of preparation; that the Editorial Board was giving further consideration to the possibility of publishing summaries of original articles in Interlingua; that the Editorial Board had reconsidered the matter of publishing the College News Notes in a separate bulletin and almost unanimously recommended the retention of the News Notes in the ANNALS proper, as at present; that the circulation of the ANNALS continues to grow, now being in excess of 17,000 copies monthly; that the paid pages of advertising in the March, 1954, issue were more than 50% greater than in the issue one year previous, and that the number of color pages had more than doubled; that the change in the cover and in the paper stock of the ANNALS had been initiated January, 1954, had been observed carefully and that the Editorial Board now recommends an even better quality of coated paper beginning with the July, 1954, issue; that the Committee does not at this time recommend wire stapling the ANNALS as a substitute for sewing, even though it would result in considerable saving; that the Board of Regents give consideration to the publication of a few selected Clinical Pathological Conferences from the Annual Session Program; critically evaluating all advertising material and all applications of exhibitors for the planning of the Clinical Pathological Conferences. In conclusion, the Editorial Board expressed its approval of the editorial policies of the ANNALS and its gratification with the excellent conduct of affairs in the office of the Editor and in the office of the Executive Secretary.

Growing out of the above recommendations, the following actions were taken:

(1) Publication of the College News Notes shall continue as heretofore in the journal itself.

(2) The Editor and Executive Secretary were directed to obtain for the ANNALS a better and heavier grade (55 lb.) coated paper, beginning July, 1954, and an appropriation of up to $16,000.00 a year for excess cost was authorized.

(3) Consideration of the suggestion concerning publishing the Clinical Pathological Conferences and setting up a special committee was deferred for later action.

A report was received from Dr. George Morris Piersol, Chairman of the Committee on Technical Exhibits, stating that the Committee had followed a policy of critically evaluating all advertising material and all applications of exhibitors for space. The Committee had visited each and every exhibit at the current meeting and was of the opinion that the Technical Exhibits were dignified, informative and appropriate. Furthermore, the Committee, with certain officers of the College, had met with the exhibitors for the purpose of discussing together criticisms or suggestions.

Dr. A. B. Brower, Chairman of the Committee on Finance, made a detailed report, including the report of the auditor for the year 1953.

REPORT OF MEETING OF THE BOARD OF REGENTS

April 9, 1954

The third meeting of the Board of Regents of the American College of Physicians, during its 35th Annual Session, was held at Chicago, Ill., April 9, 1954, with Dr. Cyrus C. Sturgis, newly inducted President, presiding and Mr. E. R. Loveland acting as Secretary. This was the organization meeting of the new Board and there were 16 Regents in attendance.

The first item on the program was a general forum for the discussion of various insurance plans of the College. Messrs. Ralph O. Claypoole and F. Wells McCormack of the Association Service Office, which handles the College insurance plans, were present to give information and to answer questions. The Board of Regents added to the Group Health and Accident Plan and the Malpractice Insurance Plan an additional Group Insurance Plan for the Dread Diseases.

Dr. Walter L. Palmer, Chairman of the Editorial Board, re-presented the suggestion of a Central Committee on Clinical-Pathological Conferences, action having been deferred from the previous meeting of the Board. After extended discussion, there developed divergent opinions and no action was taken.

Dr. Palmer, also as Chairman of the American Board of Internal Medicine, made a brief report and announced that Dr. Thomas M. Durant, Philadelphia, and Dr. John Minor, Washington, had been re-elected as representatives of the American College of Physicians for additional terms of three years, to June 30, 1957.

The Secretary, Mr. Loveland, presented a proposed small certificate in a leather bound cover to be issued to past Officers, past Regents and past Governors with a record of their service thereon recorded. The certificate with some alteration in its wording, was adopted and the Secretary instructed to proceed with the preparation and distribution of the certificates.

The Secretary was also asked to report on progress on his investigation of academic regalia for the Convocation, particularly for the President of the College. The matter had been investigated partially, but certain information was still to be obtained from the Royal College of Physicians of London. Practices of the American College of Surgeons with regard to the use of special robes was discussed. The Secretary was requested to continue the study and further report at the November, 1954, meeting of the Regents.

Dr. William D. Stroud, A. C. P. representative, reported for the American Council on Rheumatic Fever, stating that Dr. Currier McEwen and he, as representatives of the College on this Council, had attended three meetings during the year, and that they felt jointly that the Council has produced some commendable results, the chief results being included in publications which were distributed to the Regents.

Appropriations totalling $18,675.00 were added to the budget for 1954, to cover increased cost of 55 lb. coated paper in the Annals of Internal Medicine, the salaries of two new men on the College Staff in the Executive Offices, and a $100.00 donation to the National Society for Medical Research.

Dr. T. Grier Miller, Philadelphia, was officially appointed to represent the American College of Physicians at the 8th General Assembly of the World Medical Association at Rome, Italy, September 26 to October 2, 1954.

Dr. LeRoy H. Sloan was re-appointed as a Commissioner of the American College of Physicians on the Joint Commission on Accreditation of Hospitals for a three-year term, ending in 1957.

Dr. Richard A. Kern and Dr. William D. Stroud were re-elected Secretary General and Treasurer, respectively, for 1954–55.

In accordance with regulations of the By-Laws and/or regulations of the Board of Regents, Committee personnel was appointed for the current year (personnel of

the various Committees has already been published in this journal and is not now repeated).

Formal invitations were received from Minneapolis, San Francisco and Los Angeles for the College to hold its 1956 Annual Session in one of those cities. After review of facilities and hearing the invitations, Los Angeles received the largest number of votes and was selected for the 1956 meeting site. The dates set were April 16–20, inclusive, and Dr. George C. Griffith, Los Angeles, was elected General Chairman of the Session.

By resolution, the American College of Physicians withdrew from representation on the Advisory Board, American Foundation of Occupational Health.

THE PRESIDENT'S REPORT *

LeRoy H. Sloan, F.A.C.P.

Mr. Chairman, Fellows of the College, Associates, Distinguished Guests and Friends:

It seems but yesterday that the Board of Regents and the members of this College graciously accepted me as president, and entrusted to me the guardianship of its destinies, for good or for evil, till tomorrow doth end my sojourn in office.

It has been a great honor and privilege and a deeply appreciated pleasure. Whatever good has been written into the archives has been due to the whole-hearted help which has been given by your Regents, your Governors and the members of this splendid organization. I do not speak merely to use words but born of a studied conviction that in this College we have have gathered together as loyal, devoted and courageous a group of professional gentlemen as can be found any place. Whatever evil has been scratched into the record must be written against my name alone.

In the past the President's oration has been given during the convocation. This year your Regents kindly permitted me to experiment with the presentation of a more factual type of address, and the committee on streamlining the convocation gave a hearty nod. As you have no doubt observed during the past year, I have assigned specific tasks to vice presidents and they have come through—Dr. Strong, on the conduct of the convocation backed up by our splendid marshal, Dr. McGee, who has handled all of the many duties which engage a perfectionist mind and which many times pass unrecognized. To both, my heartfelt thanks. Dr. Burgess, along with Dr. Middleton, has handled the work of the joint commission with productive thought and a fine sense of the position which we occupy. Dr. Chaney is now engaged in a study with a committee of realists of our relation to economic conflicts voiced by many. Some of our members have suggested that all of these experimental changes will caption this convention as frustrated confusion, and the end result as "operation broke."

This College came into being (1913) at a peculiarly opportune period. Medicine was on the move. Medical schools were in active process of regeneration or obliteration. The good ones stood up and the ones which had lost sight of the fundamental purpose of a medical school, to teach men and women to heal the sick in all areas of the world, were obliterated. Standards of practice were elevated, the minimum standard for hospital operations, both professional and ancillary, was brought to the attention of hospital people far and wide—hospitals improved until we have reached a level of efficiency not known before. But this must not be a level of placid pleasure. Progress is not made by too long a pause, no matter how much it refreshes, progress is not an accepted automatic operation. The uncertainty of the certain is about all

* Presented at the Third General Session, Chicago, April 7, 1954.

of the laws of constants left. And there is no final end in sight. Your College cannot remain in statu quo. It must be a dynamic body which cherishes the heritage of the past, accepts the import of sensible current change for good and some plan for the future. Times change, methods change, attitudes change, but the primary objective of continuous medical education does not change. It is that the patient may receive, as a human being, competent and intelligent service. Medicine and music have been partners but also medicine and religion. It is likely that we all need not only to continue our medical education, but also to observe and practice the compulsive ethics of spiritual dependence.

Just to the south of this room, under the stands of Stagg Field which had echoed to the restless tread of young students—man brought forth an instrument of boundless potential for good or evil, a reaction which we all fervently hope will forever bear witness to the effort of physicians throughout the ages to conquer disease and which can be harnessed to the chariot of courageous and honest action but not mass destruction.

But our house engages more specific and practical thought. The College grows. The problem is one of selection. We have no restriction. We need wholesome thought in order that we do not close the gates to competent, honest bedside physicians by the quirk of a technical rule. There is nothing worse than the total frustration of a qualified man in large or small communities held bound by a technicality from which there is no appeal. I attest to the high degree of devotion to the competence, to the honesty, to the courage of our Credentials Committee. They need no defense from me. They do need the wholesome assistance of every one of our members.

This College is an institution worthy of your support and vigorous participation. The singular devotion of distinguished leaders and officers needs no elaboration.

The prestige of your organization mounts and the sphere of influence pushes back and back the boundaries of yesteryear.

The corporate responsibility increases more and more that we may shepherd this heritage of which we speak and which has been transferred to us for the moment. That that leadership in internal medicine may not be quarantined, rendered sterile or kept in containment makes incumbent upon you an appreciation of the position and objectives of your College.

The membership of your College is 16 Masters, 5,663 Fellows, 2,540 Associates. Each year we add a few more—218 Fellows and 473 Associates since the last annual session.

The assets of the College increase by wise investment and now total over one million. But recently we have assigned over thirty thousand dollars to the operation of the Joint Commission for the Accreditation of Hospitals. One of the problems before medical practice is the position of the internist in the pattern of day to day work in hospitals other than teaching hospitals. Our worker with the joint commission, Dr. John Hinman, will devote a goodly portion of his time in a study of the actual situation under the direction of the joint commission.

Without exception the regional meetings have been excellent the country over, from California to the east coast and from the south to the north. Please keep them up. Support them.

Our Conference Committee, which is now known as the Resident Review Committee, is at work in a realistic way with situations of resident training. We have thought in the past that the committee has lacked that indefinable quality called oomph. Under our genial friend, Dr. Wakefield, and the sparkplug of this convention, it has turned on the juice with a chain reaction which we expect will be genuinely productive.

Today was added, by a patient of mine, another traveling fellowship. There

are many among us who wish to do something of objective value for younger men. Here is the opportunity. I would like to see many, many more added by patients in recognition of services by their physicians, but fundamentally that they may be the agent of continuing education in medicine for some young man.

With the rapid developments in medical education and practice and especially in radioactive materials it is likely that most of us, and especially our younger group away from teaching centers, would profit by a carefully designed course. Not to make two week specialists, but to be alert to progress and cognizant of the place for such materials in therapy. I have suggested elsewhere the development in geographically focal points in this country of courses with paid instructors and with a completely adequate charge which will provide a survey of two fields—one of basic science and current change and one in the application of radioactive materials.

Recently your College has appointed an Historian, Dr. George Morris Piersol, of Philadelphia, who will begin to gather data on the history of the College and bring it up to date. Also, recently, under the will of the late Charles F. Martin, of Montreal, a legacy has been established to provide either an oil painting or an appropriate decorative feature for the Reception Room at the College Headquarters. For those of you who wish, Mr. Loveland's portrait in oil is on view in the Secretary's Office.

I cannot leave this little discussion without thanking you one and all for your active interest during the past year.

MINUTES OF THE ANNUAL BUSINESS MEETING

CHICAGO, ILL., APRIL 8, 1954

The Annual Business Meeting of the American College of Physicians was held during its 35th Annual Session, Thursday, April 8, 1954, at two o'clock p.m., in the Ballroom of the Conrad Hilton Hotel, Chicago, Ill. Dr. LeRoy H. Sloan, President, presided and Mr. E. R. Loveland was Secretary.

PRESIDENT SLOAN: The 1954 Annual Business Meeting of the American College of Physicians will come to order. I declare a quorum present.

The Secretary will read Abstracted Minutes of the preceding Annual Business Meeting.

. . . The Secretary, Mr. E. R. Loveland, read Abstracted Minutes of the 1953 Annual Business Meeting, which, by resolution, were approved as read. . . .

PRESIDENT SLOAN: Next on the agenda is the announcement of awards by the Chairman of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis.

DR. STURGIS: Mr. President, Fellows and Masters of the College: There were six Research Fellowships recommended and approved by the Board of Regents on November 15, 1953, and these men will begin work on July 1, 1954. They are as follows:

(1) *Dr. Robert Shields Abernathy*
Age, 30; a graduate of Duke University School of Medicine, 1949; to work under Dr. Wesley W. Spink, University Hospitals, Minneapolis, on studies on the pathogenesis of brucellosis along two general lines: (1) rôle of the reticuloendothelial system; (2) rôle of brucella endotoxins; $3,500.00.

(2) *Dr. Leon Cander*
Age, 27; a graduate of Temple University School of Medicine, 1951; to work under Dr. Julius H. Comroe, Jr., in the Department of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine,

on clinical physiology, with emphasis on cardiopulmonary physiology and its application to problems in internal medicine; $3,500.00.

(3) *Dr. Margaret Ann Hunt*
Age, 27; a graduate of Washington University School of Medicine, 1951; to work under Dr. Nathan B. Talbot, Massachusetts General Hospital, Boston, Mass., on homeostatic aspects of the care of patients with advanced nephritis; $3,000.00.

(4) *Dr. Harry Thurman McPherson*
Age, 27; a graduate of Duke University School of Medicine, 1948; to work under Dr. Frank J. Engel, Duke Hospital, Durham, N. C., on a quantitative study of ketone metabolism in the human by utilizing the technique of hepatic vein catheterization; $3,000.00.

(5) *Dr. Donald Hermann Walters (Alfred Stengel Research Fellow)*
Age, 32; a graduate of the University of Wisconsin Medical School, 1950; to work under Dr. A. K. Solomon, Biophysical Laboratory, Harvard Medical School, Boston, Mass., to investigate the effect of calcium and magnesium on the sodium and potassium transport in the human erythrocyte; $3,500.00.

(6) *Dr. Joseph Anthony Wilber*
Age, 28; a graduate of Harvard Medical School, 1952; to work under Dr. Eugene B. Ferris and Dr. Albert A. Brust, Grady Hospital (Emory University School of Medicine), Atlanta, Ga., to study the rôle of the autonomic nervous system in regulating the "responsiveness of the blood vessels" to circulating pressor agents in man; $3,500.00.

There were two A. Blaine Brower Traveling Scholarships for 1954, as follows:

(1) *Dr. Richard N. Frohner, Great Falls, Mont. (Associate, ACP)*
Presently with Dr. Peter Forsham at the University of California Hospital, San Francisco, Calif., observing and studying clinical and laboratory endocrinology and the work of Dr. Forsham; March 15 to April 15, 1954.

(2) *Dr. Carroll M. Leevy, Jersey City, N. J. (Associate, ACP)*
Spent month of March, 1954, with Dr. Charles H. Best, Department of Physiology and the Banting and Best Department of Medical Research, University of Toronto, observing experimental studies in liver disease, with particular reference to carbohydrate disturbances in hepatic disease and the pathogenesis and sequelae of the fatty liver.

There were a total of nine Latin-American Fellowships granted for 1953–54, as follows:

(1) Dr. Ricardo Abugattas Jasaui, Research Assistant, Cardiac Center Hospital Dos De Mayo, Lima, Peru.
(2) Dr. Jorge Espino Vela, Assistant Physician, Congenital Heart Disease, National Institute of Cardiology, Mexico, D. F.
(3) Dr. Hugo Garcia Urtubia, Clinical Assistant, University of Chile School of Medicine, Santiago, Chile.
(4) Dr. Alejandro Kuzmanic Yerkovic, Assistant, Medical Section "B", Hospital del Salvador, Santiago, Chile.
(5) Dr. Camilo Larrain Aguirre, Assistant and Hematologist, University of Chile School of Medicine, Santiago, Chile.
(6) Dr. Decio de Oliveira Penna, Assistant, Sao Paulo Faculty of Medicine, Sao Paulo, Brazil.
(7) Dr. Carlos Perez, Assistant Director, Instituto de Nutricion de Central America y Panama, Guatemala, Guatemala.

(8) Dr. Guillermo Repetto Dapelo, Pediatrician, Hospital Clinico Regional, Seguro Obrero and Unidad Sanitaria, Concepcion, Chile.
(9) Dr. Armando Silicani, Instructor in Medicine, University of San Marcos Faculty of Medicine, Lima, Peru.

There were three Postgraduate Scholarships for Residents in the amount of $1,000.00 each, per annum, granted by the Committee, approved by the Board of Regents on April 7, 1954, and provided by the Mead Johnson Postgraduate Scholarship Fund, as follows:

(1) Dr. Joseph F. Dingman, nominated by Governor Richard P. Stetson of Massachusetts.
(2) Dr. Morton Bogdonoff, nominated by Governor Elbert L. Persons, North Carolina, and sponsored by Dr. Eugene A. Stead, Jr., F.A.C.P.
(3) Dr. Leighton E. Cluff, nominated by Governor R. Carmichael Tilghman, Maryland.

We also announce the establishment of the Elizabeth Archbold Bowes Memorial Traveling Scholarship, which has been given by Mrs. Margaret Bowes Murphy, Chicago, Ill., a patient of Dr. LeRoy H. Sloan. She has delivered to the College $400.00 for the support of a Brower-type Traveling Scholarship starting in 1954, to be continued for several years. The Scholarship is established in memory of her mother, Elizabeth Archbold Bowes, and is restricted to candidates from Canada.

President Sloan: Next will be a report on the Group Insurance Plans of the College by Mr. F. Wells McCormack of the Association Service Office.

Mr. McCormack: Your Insurance Committee has suggested a general report at the end of the first year of operation of the Group Insurance Plans to its members.

To the Health and Accident Plan, applications were received from approximately 3,500 members; claims were paid to 339, these claims amounting to slightly over $102,000.00. Claims, naturally, are still being made. In some cases benefits are continued on prior claims; some claims are awaiting the necessary report forms. The carrier has established approximately $150,000.00 as a reserve to cover unknown and continuing claims. Therefore, at the end of the first year, we have paid, or set up reserve for payment, approximately $250,000.00 for this organization.

The largest amount paid to one individual was approximately $2,400.00; the smallest, $17.00. That illustrates the widespread benefits to our members.

We have an important announcement to make. The College Group Plan for Health and Accident closed for unrestricted subscriptions on July 11, 1953. Since that time, there have been received many letters and requests from members who for one reason or another mislaid material and did not submit their applications during the subscription period. It is believed that there are a great many who still desire an opportunity to join the Plan. We are gratified to announce that the insurance company has agreed to reopen the Health and Accident Plan for unrestricted subscription, provided applications are filed between April 5 and June 15, 1954. All applications filed before April 15 or between April 15 and May 15 will have an effective date of April 15 and will bear the full annual rate; applications filed between May 15 and June 15 will have the effective date of May 15, and the premium will be prorated for eleven months. Your special attention is called to the fact that on June 15, 1954, the Plan will definitely be closed to unrestricted subscription. The insurance company has definitely announced that it will not again reopen the Plan to unrestricted subscription until the end of the initial five-year period, so that at that time they may definitely determine the trend of our claim ratio. The claim ratio at present is quite satisfactory. No one can tell what five years will show. Some claims entered the past year will undoubtedly run a full five-year term.

The Professional (Malpractice) Group Plan. Up to this time less than 1,000 members have been insured. It was not anticipated that the Malpractice Plan would grow as rapidly as the Health and Accident Plan. Many members already had three-year policies; some had other malpractice policies that had to expire before they made application for the College Plan. Applications are increasing, and we are receiving between 80 and 100 new applications each month.

I wish to emphasize the fact that the College rates are becoming increasingly attractive, because other companies have constantly increased, in recent months, their malpractice rates. We are informed that in some localities, rates have been increased as much as 100 per cent. It is to your interest, before you renew your old policy, to examine the new rates and to compare them with those under the College Plan. If we secure adequate participation of members in the College Plan, the underwriters have given a guarantee that the rates will automatically be reduced as long as the loss ratio remains favorable. Thus far, we have had no known losses. We have had four cases or possible claims reported, each of which was terminated within two weeks time without specific claims developing and without expense to our Plan. We believe the College constitutes a select group and should earn reduced premiums. Because we had no claims up to January 1, 1954, the underwriters granted us substantial reductions in the upper limits of protection—that is, on limits of $25,000.00 to $150,000.00. They also authorized the writing of coverage up to $300,000.00, which was denied under the original Plan.

This is a very favorable indication; the underwriters are working with us.

We can only keep these Plans growing by the support of the members of the College. We can only fight the Malpractice situation throughout the country by concerted effort of the members. We must have your support, as shown through your applications, to accomplish the best results.

PRESIDENT SLOAN: We should protect ourselves against sickness. Get yourselves insured when you can and for as much as you can, and then we should teach our students that when they go out to practice medicine to get adequate protection against malpractice.

Next report will be the Annual Report of the Treasurer, Dr. William D. Stroud.

DR. STROUD: Mr. President, Masters and Fellows of the College:

The detailed Statements of Operation of the College for 1953, along with the Certified Public Accountant's report, will be published in an early issue of the ANNALS OF INTERNAL MEDICINE.

During the year 1953 the College added to its General Fund $83,593.80, to its Endowment Fund $29,722.61 and to its Restricted Funds $137.90, or a total of $113,454.31.

The Gross Assets of the College, as of December 31, 1953, amounted to $1,103,897.29, divided as follows:

Endowment Fund	$ 412,321.25
James D. Bruce Fund	10,000.00
A. Blaine Brower Fund	20,000.00
General Fund	660,149.32
Restricted Funds	1,426.72
	$1,103,897.29

The College operated wholly within its Budget. Income was in excess of budgetary expectations, whereas Expenditures were actually less than the appropriations. The investments of the College and the custodianship of such investments are supervised by a competent and reliable Investment Counselor, with whom the Committee on Finance maintains close contact and direction. As of December 31, 1953, the College held investments at Book Value totalling $962,105.34, which, as of March

15, 1954, had a current market value of $1,159,300.00, or an appreciation of $197,-194.06. The average yield for 1953, based on current market value, rather than book or cost price, was 4%, a slight improvement over the preceding year when it was 3.87%.

The Board of Regents has approved a Budget for 1954 calling for an estimated Income of $372,600.00 and estimated Expenditures of $320,764.00, leaving an estimated balance of $51,835.00.

The financial policies of the College and of the Committee on Finance are conservative and administered with diligence and care.

Respectfully submitted, William D. Stroud, Treasurer.

. . . By resolution unanimously adopted, the Annual Report of the Treasurer was accepted. . . .

PRESIDENT SLOAN: The next matter on the agenda is the Annual Report of the Executive Secretary, Mr. E. R. Loveland.

MR. LOVELAND: Mr. President, Masters and Fellows of the College: This report is merely supplementary to those of the President, the Treasurer and the Secretary-General.

We believe the American College of Physicians to be the most serviceful medical society in the world, with the exception of the American Medical Association. Its administration twenty-eight years ago was comparatively simple, because the major activities consisted of handling candidates for membership, publishing a small journal and conducting an Annual Session. With each succeeding year, new activities have been added and old ones expanded. Today there is the general administration; management of more than a million dollars in securities; accounting; journal publication and circulation, excelling that of any publication in its field; a tremendously expanded Annual Session; twenty-five to thirty Regional Meetings annually; operating a postgraduate program for one thousand to twelve hundred physicians; property management; educational and public relations; a broad fellowship program for Research Fellows, Latin-American Fellows, Brower and Mead Johnson Scholars; Directory publication; a very large annual Technical Exhibit; an extensive insurance program for our members, both with regard to Health and Accident and Malpractice; cooperating programs with the Joint Commission on Accreditation of Hospitals, the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association, and numerous other activities of lesser proportions, but, nevertheless, time and energy consuming.

Twenty-five years ago we had less than a half dozen active Committees; today there are no less than twenty-five, most of which are very definitely active. The details of the accomplishments of these Committees, in very abridged form, comes to the members through the reports of the various Officers, the Board of Regents and the Board of Governors, either at these meeting, or through the ANNALS OF INTERNAL MEDICINE. The work of one of the newer Committees, that on insurance, deserves some special mention not covered by the reports of other Officers. One year ago the Board of Regents adopted a Group Plan of Health and Accident Insurance for the members, to which more than fifty per cent of the eligible members have subscribed. We have been impressed, first, by the reasonable premiums that have been established; second, by the fact that 289 claims have been made and more than $101,129.62 have been paid on such claims. It has amazed us how many members who were in apparent good health a year ago have been stricken by disabling conditions, some of which are for life, and to whom these benefits have been truly a godsend. The Health and Accident Plan, we believe, has been eminently successful and satisfactory. It is available to new members, provided they subscribe within two months after receipt of official notification of election, and more gratifying, perhaps, is the fact that the carriers have agreed to reopen the Plan from April 5 to June 15 to the old members who didn't take advantage of the Plan during the qualifying period last year. The

Malpractice Plan, taken through American underwriters for Lloyds of London, is a worthy, fine Plan for our members. Unfortunately, the promoters of more restricted regional plans in the United States have opposed the College Plan and attempted to arouse uncertainty in the minds of our members in some areas. This, undoubtedly, has had a deterring effect upon the number of members who have subscribed, in spite of the advantages in premium and other considerations. Some are fearful that immediate counsel and protection would be delayed, because they look upon the carrier as a foreign institution. Claims have been exceedingly few, limited to only two or three cases, and in those cases the carrier was immediate and prompt in servicing the claims and protecting the member. We have no substantiation whatsoever or proof that the Group Malpractice Plan adopted for the College is illegal to our members wherever they may be, nor have we any reason to doubt that every subscriber will receive full and prompt protection. We may add that it is our observation that Malpractice Insurance is in a state of flux the country over, that companies are raising premiums on renewals everywhere as a protection to themselves against the ever increasing number of malpractice suits. In the case of the plan adopted by the College, rates have actually been adjusted slightly downward, but to maintain this position, a much larger proportion of the College members should take advantage of the plan. Not nearly the required number have, up to the present, subscribed, but a few new applications still continue to come in. Unlike the Health and Accident Plan, the open period for subscription will extend through the current year, in an attempt to obtain the necessary number of subscribers.

The College Committee on Exhibits has presented to you at this meeting a fine Technical Exhibit, and the largest in the history of the College. We bespeak your support by spending some time inspecting them. It is the income from our exhibits and from our journal which has supported a great many of the College activities and has made it possible to keep the dues at the low level they were twenty-five years ago.

The Committee on Postgraduate Courses has continued their very outstanding program; the circulation of our journal continues to expand; more and more of our Fellows become Life Members; Regional Meetings continue to be a popular and beneficial activity, conducted by the Governors in the various States and Provinces; our Research Fellowships, Latin-American Fellowships and Brower Scholarships are all highly productive, and the results gratifying; during this past year an entirely new and revised Directory, of nearly a thousand pages, has been published; this Annual Session has further extended the interest and participation of our members; the Officers, the Board of Regents and the Board of Governors, individually and collectively have made available to the College their unselfish efforts and service at all times—every day and at every step we have had the encouragement, advice and ready cooperation of every one of them. The General Chairman, Dr. Wakefield, the President, Dr. Sloan, and the Chairmen and members of the various Chicago Committees have done a tremendous job in organizing this meeting.

Special mention should be made that the late Dr. Charles F. Martin, Montreal, a great power and influence in the earlier years of the College as its President, a Master and Stengel Memorial Diplomate of the College, in his will bequeathed to the American College of Physicians $2,500.00 " to be used by the Board of Regents either for the purchase of a suitable painting for the Reception Room of the College Headquarters, Philadelphia, or for such other purposes they, in their absolute discretion, may see fit as a souvenir of their many kindnesses to me."

We have just received from the Registration Desk a report that the total registration at this meeting is 5,386, of which 803 are ladies.

Respectfully submitted, Edward R. Loveland, Executive Secretary.

. . . By resolution unanimously adopted, the Annual Report of the Executive Secretary was accepted. . . .

PRESIDENT SLOAN: Next will be the Annual Report of the Secretary-General, Dr. Richard A. Kern.

DR. KERN: Mr. President, Regents, Governors, Masters and Fellows of the College: My report will be limited to certain matters of particular interest to you:

Membership—Since the last Annual Session of this College, there have been elected 4 Masters, 218 Fellows, 473 Associates, which brings the total membership to the following:

Masters	16
Fellows	5,663
Associates	2,540
Total	8,219

Life Members—Since the last Annual Session of this College 91 Fellows have become Life Members, bringing the total to 1,237, of whom 124 are deceased, leaving a balance of 1,113.

Deaths—In the interim, since the last Annual Session, we have lost by death 3 Masters, 84 Fellows and 9 Associates. Their names and records appear in the Archives of the College, and their obituaries have been published, or will be published, in the ANNALS OF INTERNAL MEDICINE.

Postgraduate Courses—The Committee on Postgraduate Courses, during the autumn semester of 1953 conducted 8 Courses, with a registration of 471 physicians. During the spring term of 1954, 8 additional Courses have been scheduled, some of them over-subscribed, with an estimated registration, to the end of June, of 500.

Fellowships—Currently, the College has working 6 Research Fellows whose program will be concluded on June 30, 1954, and 6 Research Fellows who will start their program on July 1, 1954, working for one year. The work of these fellows is carefully observed, with a view to evaluating the program and to act as a guide in the future.

Also, the College has 16 Latin-American Fellows presently working in this country, this program being administered in cooperation with the W. K. Kellogg Foundation, which provides the funds. The fellows selected are, for the most part, preparing for careers of teaching and research in their homelands. The College is deeply indebted not only to the Committee on Fellowships but also to the Preceptors who really make this program so valuable.

During the present year the College has awarded 2 Brower Traveling Scholarships to Associates of the College, for the purpose of providing an opportunity to spend a month or more as visiting fellows at some institution or institutions for observation, contacts and postgraduate study. This program has been so productive and has attracted such attention that we are gratified to announce that a layman, a patient of our President, has become interested in this program and has provided funds for the founding of an additional Brower-type scholarship, to be known as the "Elizabeth Archbold Bowes" Memorial Traveling Scholarship, and to be awarded to a Canadian recipient, preferably an Associate of the College.

Further, we announce that Mead Johnson & Company, having confidence in the manner of administration and the effectiveness of fellowship programs conducted by the College, has initiated 3 Postgraduate Scholarships for Interns or Residents in Internal Medicine. This program is in the course of initiation, and it is hoped that the number of such postgraduate scholarships will be increased.

Regional Meetings—During the calendar year 1953, 27 Regional Meetings were conducted in various territories, with a total registration of over 3,100. In 1954 there have been conducted, or scheduled for the future, 17 Regional Meetings, with others to follow. The Regional Meeting programs are conducted by members of the

Board of Governors and fulfill an especially important purpose in the regional areas of the membership.

Of prime significance, however, to the membership-at-large is the Annual Session of the College. The present session in Chicago not only is an outstanding example of the accomplishments of a year's co-ordinated effort, but probably will be a milestone in the history of great Annual Sessions of the College.

Respectfully submitted, Richard A. Kern, Secretary-General.

. . . By resolution unanimously adopted, the Annual Report of the Secretary-General was accepted. . . .

DR. KERN: Dr. Sloan, since you attained Fellowship in this College 25 years ago, you have served it faithfully and well in an official career that began in 1938 with your election as Governor for Northern Illinois, and that has included service as a Regent, as General Chairman of the Annual Session in 1947, as First Vice President, President-Elect, and President. Throughout, you have entertained a realistic and practical view of the best interests of the College, and have labored early and late to promote those interests. In so doing, you have manifested personal qualities of geniality and charm that have endeared you to us all. Therefore, at this time when you are about to enter the ranks of the elder statesmen, I present to you, on behalf of the Masters, Fellows, Governors, Regents and Officers of the American College of Physicians, the Gavel of your Presidency, as a token of our grateful appreciation and as a momento of our affection and esteem.

. . . The Gavel was presented to Dr. Sloan. . . . (Applause)

PRESIDENT SLOAN: Thank you. I accept the Gavel, although I hardly recognize the individual about whom you were speaking. I have had a lot of fun doing the work of the College. I have enjoyed particularly the wholehearted and total cooperation of the Governors and of all our members, and I thank them sincerely.

It now gives me the greatest of pleasure to introduce to you your next President, Dr. Cyrus C. Sturgis. (Applause)

Dr. Sturgis, I know of no one to whom I would rather entrust the activities of this fine College for the next year than to you.

PRESIDENT STURGIS: I am very appreciative of your kind remarks, Dr. Sloan.

Now, Members of the College, Ladies, and Gentlemen, let me first thank you for having selected me as your President. The position is by itself one of honor. It is very gratifying to me to follow in the long line of my illustrious predecessors.

I want to make four points which may be of some importance to the future of this College:

(1) It is very easy to define what our function is—the furtherance of education, principally postgraduate education. Someone has said, and I think it is true, "A serious weakness in the educational process is a weakness of the link between what we have been taught in school and what we learn from practical experience after leaving school. It is not the loss of facts, but the loss of curiosity, the loss of a habit of learning that matters, and it matters tremendously." Education, then, is the essential function of this College. Let us devote ourselves intensively and almost exclusively to this major function.

(2) One of the greatest hazards to the efficiency of any organization is complacency, satisfaction with the present, instead of striving to improve. "You are doing your best only when you are trying to improve what you are doing."

(3) I present this thought for your careful consideration. When we are out of sympathy with the young, our work in this world is about over. The most important aspect of our work in the College is, therefore, the guidance, stimulation, training, and assistance of the younger members of the profession.

(4) Let me warn you that politics has no place in this organization. If this influence should ever creep in, then our main objective would become a secondary one. No truer words were ever uttered than those by David E. Lilienthal, formerly of the Atomic Energy Commission, when he said, "When politics enters, the entire edifice of our enterprise, ability, or expert skill becomes unsafe." Never was as important a truth expressed in more accurate or more terse language.

Let me say again how grateful I am to you for offering me this opportunity to serve as President and to say that this organization will have my very best effort in the coming year. (Applause)

We shall now proceed with the business of the meeting. First is the submission for approval of the Fellows and Masters of an amendment to the By-Laws, which has been formally approved by the Board of Regents, November 15, 1953. This amendment is to the By-Laws, Article XII, Annual Convocation, last sentence, which now reads: "A Presidential Address will be delivered on this occasion." The amendment recommended for adoption reads: "A Presidential Address will be delivered on, *or before,* this occasion."

. . . A motion was made and seconded and regularly adopted, accepting the amendment. . . .

PRESIDENT STURGIS: The next order of business is the report of the Committee on Nominations, Dr. Howard P. Lewis, Chairman.

DR. LEWIS: Mr. President, the Committee on Nominations, appointed in accordance with the By-Laws of the College, places in nomination the following names for the Elective Officers of the College:

President-Elect ..... Dr. George F. Strong, Vancouver, B. C., Can.
First Vice President ..... Dr. Marion A. Blankenhorn, Cincinnati, Ohio
Second Vice President ..... Dr. George H. Lathrope, Morristown, N. J.
Third Vice President ..... Dr. Ramon M. Suarez, San Juan, P. R.

. . . President Sturgis, in accordance with provisions of the Constitution and By-Laws, invited nominations from the floor. Individual resolutions for each Officer were regularly adopted electing each of the above as nominated. . . .

DR. LEWIS (Continuing): The Committee places in nomination the following name for election as a Regent of the American College of Physicians, for term expiring in 1956, to conclude the unexpired term of Dr. George H. Lathrope:

Dr. Fuller B. Bailey, Salt Lake City, Utah.

. . . President Sturgis invited nominations from the floor; there were none and a resolution was regularly adopted unanimously electing Dr. Bailey as a Regent, for term expiring in 1956. . . .

DR. LEWIS (Continuing): The Committee places in nomination the following five names for election as Regents of the American College of Physicians, for term expiring in 1957:

Dr. J. Murray Kinsman, Louisville, Ky.
Dr. Asa L. Lincoln, New York, N. Y.
Dr. Walter L. Palmer, Chicago, Ill.
Dr. Karver L. Puestow, Madison, Wis.
Dr. Wallace M. Yater, Washington, D. C.

. . . President Sturgis invited nominations from the floor; there were none and a resolution was unanimously adopted providing for the election of the above five nominees as Regents, for terms expiring in 1957. . . .

DR. LEWIS (Continuing): The Committee places in nomination the names of the following men as Governors of the American College of Physicians, for term expiring in 1955:

Dr. Rudolph H. Kampmeier, Nashville.....TENNESSEE
Dr. Theodore C. Bauerlein, Salt Lake City.UTAH

. . . President Sturgis invited nominations from the floor; there were none and a resolution was unanimously adopted electing the above two nominees as Governors, for terms expiring in 1955. . . .

DR. LEWIS (Continuing): The Committee places in nomination the name of the following man as Governor of the American College of Physicians, for term expiring in 1956:

Dr. Marion D. Hargrove, Shreveport.....LOUISIANA

. . . President Sturgis invited nominations from the floor; there were none and a resolution was unanimously adopted electing the above nominee as a Governor, for term expiring in 1956. . . .

DR. LEWIS (Continuing): The Committee places in nomination the names of the following men as Governors of the American College of Physicians, for term expiring in 1957:

Dr. D. O. Wright, Birmingham.....ALABAMA
Dr. Leslie R. Kober, Phoenix.....ARIZONA
Dr. Lemuel C. McGee, Wilmington.....DELAWARE
Dr. William C. Blake, Tampa.....FLORIDA
Dr. Carter Smith, Atlanta.....GEORGIA
Dr. Richard P. Howard, Pocatello.....IDAHO
Dr. Howard Wakefield, Chicago.....ILLINOIS (Northern)
Dr. Sam A. Overstreet, Louisville.....KENTUCKY
Dr. Richard S. Hawkes, Portland.....MAINE
Dr. R. Carmichael Tilghman, Baltimore....MARYLAND
Dr. Laurance J. Clark, Sr., Vicksburg.....MISSISSIPPI
Dr. Harold W. Gregg, Butte.....MONTANA and WYOMING
Dr. Walter I. Werner, Albuquerque.....NEW MEXICO
Dr. Irving S. Wright, New York.....NEW YORK (Eastern)
Dr. Charles A. Doan, Columbus.....OHIO
Dr. Merl L. Margason, Portland.....OREGON
Dr. David W. Carter, Jr., Dallas.....TEXAS
Dr. Frederick W. Madison, Milwaukee.....WISCONSIN
Dr. Rafael Rodriguez-Molina, San Juan....PUERTO RICO
Dr. Percy H. Sprague, Edmonton.....ALBERTA
Dr. Charles H. A. Walton, Winnipeg.....MANITOBA and SASKATCHEWAN

. . . President Sturgis invited nominations from the floor; there were none and a resolution was unanimously adopted electing the above nominees as Governors for their respective territories, for terms expiring in 1957.

President Sturgis then appointed a committee of two, Drs. Herbert K. Detweiler and Hugh J. Morgan, to escort the new President-Elect to the rostrum. . . .

. . . The President-Elect, Dr. George F. Strong, was escorted to the rostrum. . . . (Applause)

PRESIDENT-ELECT STRONG: The President's first official act was to warn me that I wasn't to speak over twenty seconds; therefore, I am forced to say, I thank you and I shall do my best.

PRESIDENT STURGIS: Newly elected Governors who have not served previously, or other Governors who may be interested, are invited to meet immediately after this meeting in the Regents' and Governors' Room with the Chairman of the Committee on Credentials, the Chairman of the Board of Governors, the President of the College, and the Executive Secretary.

Dr. Edward L. Bortz has a resolution to present.

DR. BORTZ: Mr. President, I desire to offer this resolution:

To our distinguished leader and President, Dr. LeRoy H. Sloan, for the inspiration of his guidance during the past year and for the superior program of Morning Symposia and General Sessions at this meeting;

To his Chief of Staff, General Chairman Howard Wakefield, for the organization of this meeting and for his part of the magnificent program;

To the Chairmen of the local Chicago Committees:

Dr. Edwin N. Irons, Chairman of the Committee on Auditorium;
Dr. Lowell T. Coggeshall, Chairman of the Committee on Hospital Clinics;
Dr. Edwin F. Hirsch, Chairman of the Committee on Clinical-Pathological Conferences;
Dr. Walter S. Priest, Chairman of the Committee on Entertainment;
Dr. George A. Hellmuth, Chairman of the Committee on Hotels and Transportation;
Dr. G. Karl Fenn, Chairman of the Committee on Panel Discussions;
Dr. Gerald M. Cline, Chairman of the Committee on Pediatrics;
Dr. Howard B. Carroll, Chairman of the Committee on Publicity;
Dr. Frank B. Kelly, Chairman of the Committee on Televised Clinics;
Dr. Richard H. Young, Chairman of the Medical Dean's Committee of Chicago Medical Schools,

and to the individual members of each of those Committees;

To Mrs. Walter L. Palmer, Chairman of the Committee on Ladies' Entertainment, and all of her worthy and capable colleagues;

To Mr. Fritz Reiner, Conductor of the Chicago Symphony Orchestra, for a most unusual entertainment afforded at our Monday evening Concert;

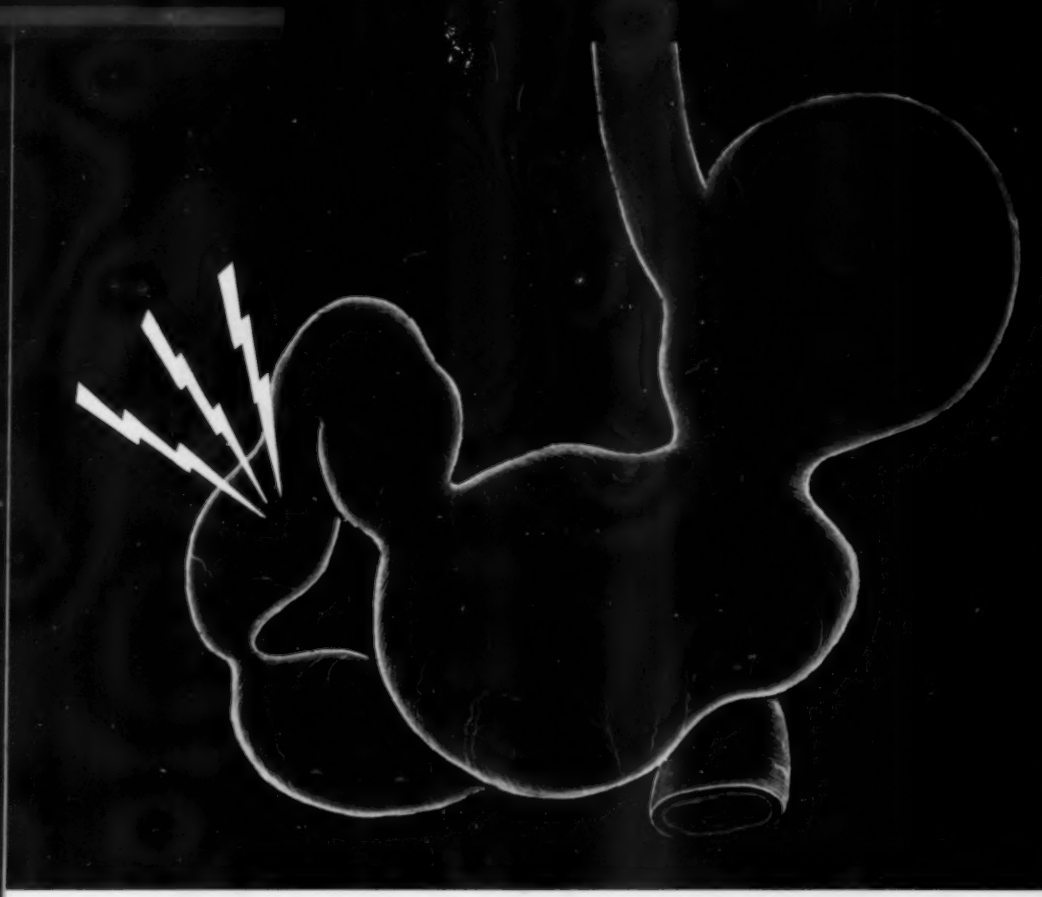
To the Chicago Convention Bureau;

To all of these and many others, individually and collectively, our heartfelt thanks again for their manifold contributions to the success of this memorable meeting and for their most generous hospitality.

. . . The resolution was unanimously adopted. . . .

Adjournment, two forty-five o'clock p.m.

Attest: E. R. LOVELAND
Secretary



Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations[1,2] on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

"... abnormal motility[2] is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

Clinical Application of Pro-Banthine®

Pro-Banthine has been demonstrated consistently to reduce hypermotility of the stomach and intestinal tract and in most instances also to reduce gastric acidity. Dramatic remissions[1] in peptic ulcer have followed Pro-Banthine therapy. These remissions (or possible cures) were established not only on the basis of the disappearance of pain and increased subjective well-being but also on roentgenologic evidence.

Pro-Banthine (Beta-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) has other fields of usefulness, particularly in those in which vagotonia or parasympathotonia is present. These conditions include hypermotility of the large and small bowel, hyperemesis gravidarum, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm.

1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

SEARLE Research in the Service of Medicine

this is the lesion that benefits from prompt...prolonged antacid action

PEPTIC ULCER AS ADAPTED FROM BOYD'S A TEXTBOOK OF PATHOLOGY, LEA AND FEBIGER, PUBLISHER

TITRALAC®

unique antacid—with milk-like action*

TITRALAC, *in vitro*, "...brought the pH up the most rapidly and to the highest level....
The sustaining power was stronger, in addition."[1]

1. Hammarlund, E. R., and Rising, L. W.: J. Am. Pharm. A. (Scient. Ed.) *41*:296, 1952.
Each tablet provides 0.15 Gm. glycine, plus 0.35 Gm. calcium carbonate.
TITRALAC IS SCHENLEY'S REGISTERED TRADEMARK FOR AN ANTACID

Schenlabs

SCHENLEY LABORATORIES, INC., NEW YORK 1, NEW YORK

54084

INDEX TO ADVERTISERS

August, 1954

your hay-fever patients will prefer

CO-PYRONIL

(PYRILAMINE COMPOUND, LILLY)

to any other antihistaminic

'Co-Pyronil' affords

rapid relief

—within fifteen to thirty minutes

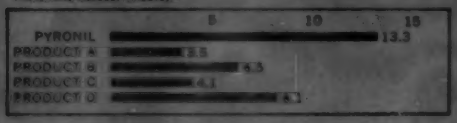
complete relief

prolonged relief

with fewer side-effects

—rarely causes sedation, even on high dosage

Maximum Duration of Effect in 50 Percent of Guinea Pigs Subjected to a Histamine Aerosol (Hours).*



Dose: 1 or 2 pulvules every eight to twelve hours.

NEW

SUSPENSION CO-PYRONIL

Taste-tested and approved by the Junior Taste Panel. Each teaspoonful of suspension is equivalent to half the formula contained in one Pulvule 'Co-Pyronil.'

*Proc. Soc. Exper. Biol. & Med., 80:458, 1952.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Editorial Office—University Hospital, Baltimore 1, Maryland

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material should send it to the Editor. Since it is not possible to review all books submitted, a monthly list of all those received will be published in the review section.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: $10.00, United States, Canada, Hawaii, and Puerto Rico; $7.00, in the above countries, to bona fide medical students, interns and residents; $11.00, other countries. Prices for back numbers furnished upon application. Single numbers, current volume, when available, $1.25. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

LANCASTER PRESS, INC., LANCASTER, PA.